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## ORIGINAL ARTICLES.

### THE EFFECT OF AGE ON THE SUSCEPTIBILITY OF THE ERYTHROCYTE TO HYPOTONIC SALT SOLUTIONS.

### RADIOACTIVE IRON AS A MEANS OF TAGGING THE RED BLOOD CELL.*

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The difference in susceptibility of red blood cells to hemolysis by hypotonic salt solution has been ascribed to a number of factors, among which are variations in osmotic resistance, varying degrees of permeability of the erythrocyte membrane, brought about by various causes including difference in the age of the red cells. At present it seems well established that the shape of the cell, or more explicitly the ratio between the thickness and the diameter, is the most important factor.[3,6,9,19]

Convincing data regarding the rôle played by age of the erythrocyte as regards hemolytic susceptibility are not found in the literature of this subject. Some investigators find the morphologically immature red cells (reticulocytes, granulated red cell forms) more resistant to hypotonic salt solutions than the adult erythrocytes.[1,14,20,21,23,24] Others find a decrease in the susceptibility of the same cell forms.[4,5,8] Still others find no difference between the

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immature and the adult forms.[16–18,22] Buckmann and MacNaugher found that the young cells were less resistant in pernicious anemia and more resistant in anemia after hemorrhage.[2] Daland and Zetzel[7] concluded that the age of the erythrocyte does not necessarily determine its behavior in hypotonic salt solution. They found the young cells (reticulocytes) more, less, or equally resistant than the adult cells in different diseases and even in the same patient with pernicious anemia in different regeneration periods following liver therapy. All such studies must necessarily be limited to the determination of different susceptibilities between reticulated or granular forms and the general run of the erythrocytes in the circulation, since no other means were available to determine the age of the cells than by histologic methods.

When the radioactive isotope of iron is administered to an anemic animal, some of it is very promptly used to form hemoglobin in the red blood cells.[13] This iron when bound in hemoglobin within the cell does not undergo exchange with the other iron of the body,[12] and so affords a means of identifying the new cells as distinguished from those red cells which were present before and made up the bulk of the circulating cells. If a comparatively small amount of the iron is given as a single dose to an animal, the age of the red cells into which it is incorporated can be estimated to within a few days.[13] This enables one to distinguish between cells of known ages ranging from a few days to several months and the general run of the cells in the circulation.

**Methods.** To determine the resistance of the erythrocyte, amounts of whole blood were added to salt solutions of varying concentrations, the proportions being the same for any one experiment and usually being in a ratio of 1:5. The actual amount of whole blood used depended upon the concentration of activity.

In a typical experiment 15 ml. of freshly drawn whole blood were added to each of a series of tubes containing 75 ml. of, respectively, 0.50, 0.45, 0.40, 0.35, 0.30% NaCl solutions and one tube with distilled water. After contact of about 20 minutes, the suspensions were centrifuged. The supernatant solutions were separated from the cells by suction. Aliquots of the supernatant solution were diluted with distilled water to permit reading in a Klett photoelectric colorimeter. These values, when related to the reading of completely hemolyzed cells (distilled water), represented the percentage hemolysis for each concentration of salt.

The supernatant solutions were separately ashed,[10,11] the iron precipitated and a determination of the radioactivity made.[13] The activity was expressed as a fraction of that obtained from the supernatant of the cells treated with distilled water. Since only the radioactive cells contributed to this value, it is a measure of the hemolysis of the cells of known age due to labelling with the isotope.

**Experimental Observations.** In the preliminary experiments, anemic, iron-depleted dogs were employed. In these animals, due to the often repeated removal of large quantities of blood, the mean age of the red cells in the circulation is probably a matter of a few weeks, this depending on the frequency with which all the circulat-

ing cells are completely replaced by erythropoiesis. Therefore, the differences in age of the new tagged cells and general run of the red cells could be considerable only in the first few days of the experiments. Later normal animals were used, being subjected to two bleedings equivalent to about two-fifths of their blood volumes in order to stimulate hemoglobin formation shortly before the injection of the iron containing the radioactive isotope.

In Experiment 1, Dog 39-226, an adult, female mongrel setter weighing 10 kg., was depleted of iron reserves by repeated bleeding and the anemia was maintained in this way for 5 weeks' time. A series of 5 injections of ferric ammonium citrate containing the isotope were given. These were administered on successive days and consisted of 55 mg. of iron each. Seven days after the first and 3 days after the last injection, blood was withdrawn for determination of susceptibility toward salt solutions of various concentrations and the corresponding radioactivity of the remaining red cells and supernatant layers was measured. The animal was not disturbed for 9 weeks after which measurements were repeated (Chart 1).

Experiment 2 concerns Dog 38–137, an adult, female beagle, weighing 10 kg., which likewise had its iron reserves exhausted by an anemia of 6 weeks' duration. This animal was given a single injection of the radioactive iron by vein consisting of 71 mg. of the element in the form of ferric ammonium citrate. At this time, the blood hemoglobin level was 6 gm. per 100 ml. Three days later, blood was withdrawn for determination of hemolytic susceptibility and radioactivity. Unfortunately, the activity of the cells as measured was exceedingly low and as the results are not very good from a quantitative standpoint, they are not included. Under these conditions, it would be necessary to employ larger quantities of blood to establish the various points with precision. The same animal was allowed to continue for a considerable period subsequently in one of a series of experiments involving the determination of the life cycle of the red cell. At the end of 124 days, a single blood sample was taken and the hemolysis of the cells in saline studied (Table 1).

TABLE 1.—SUSCEPTIBILITY OF 4-MONTH-OLD CELLS.

Dog 38–137.

| Age of tagged cells, days. | Conc. hypotonic sol., per cent. | Hemolysis of all cells (colorimetric), per cent. | Hemolysis of tagged cells (radioactivity) per cent. |
|---|---|---|---|
| 124 | 0.41 | 63 | 44 |
| 130 | 0.36 | 92 | 82 |
| 130 | 0.39 | 66 | 45 |
| 130 | 0.42 | 34 | 29 |

Six days later, three equal aliquots of blood were treated with salt solutions of concentrations of 0.36, 0.39, and 0.42% and the hemolysis of the tagged cells and of the total cells determined.

Experiments 3 and 4 were conducted on animals which previous to the experimental work had been normal stock dogs. Dog 40–115,

an adult mongrel, weighing 16.7 kg., was bled about 200 ml. on each of 2 successive days. Immediately following the second bleeding, 125 mg. of iron as ferric ammonium citrate was injected by vein. Four days later, blood was withdrawn for determination of susceptibility to salt solutions and measurement of radioactivity. As can

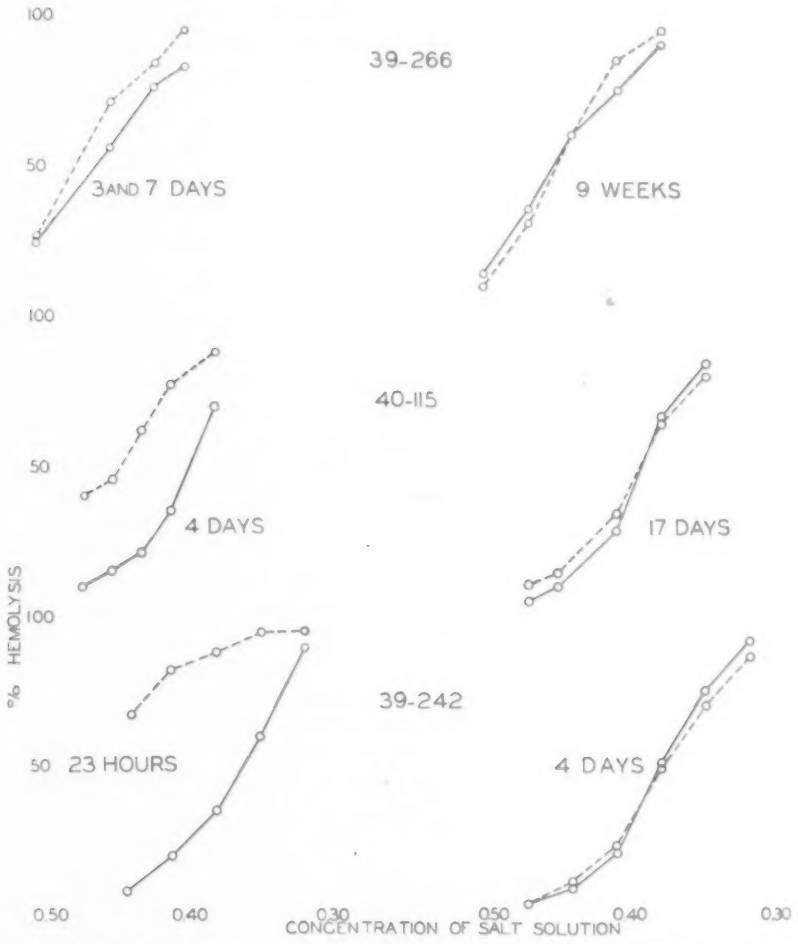


CHART 1.—Susceptibility at various known ages. o————o, hemolysis of all cells (colorimetry); o - - - - o, hemolysis of labelled cells (radioactivity).

be seen in Chart 1, the curves for hemolysis of the cells in general, and the hemolysis of the tagged cells as measured by the radioactivity of the supernatant solutions, are widely divergent. Seventeen days after the injection of iron, blood was again drawn for these determinations and the curves are nearly identical.

Dog 39–242, a normal, adult mongrel, weighing 11.7 kg., was bled 250 ml. on each of 2 days and immediately after the latter bleeding was given an injection of 31 mg. of iron containing the isotope as ferric ammonium citrate by vein. In order to see if the divergence of the curves for total hemolysis and the radioactivity of the supernatant solutions would be more marked than in the 4-day experiment above, blood was taken for measurements after only 23 hours had elapsed. In Chart 1, the marked dissimilarity of the two curves can be seen. Four days after the injection, another sample of blood

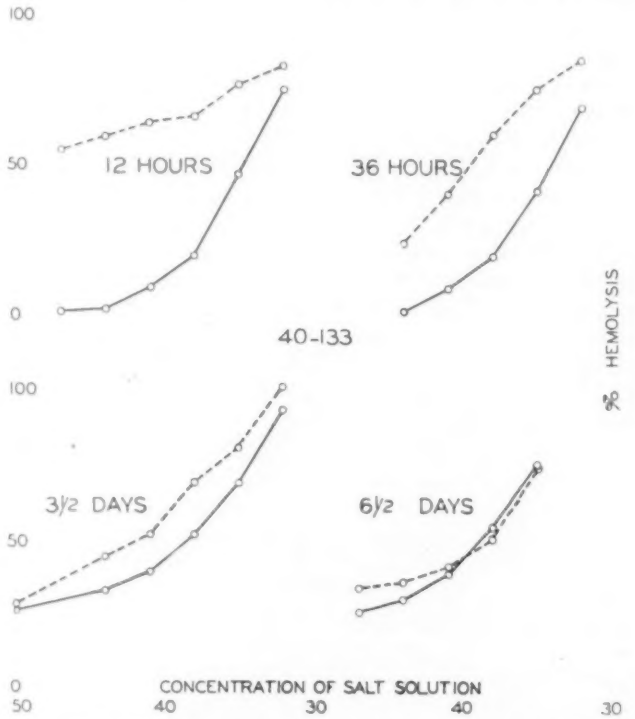


CHART 2.—Susceptibility decreases with age. o————o, hemolysis of all cells (colorimetry); o – – – – o, hemolysis of labelled cells (radioactivity).

was withdrawn for measurement, and it was found that the two curves were superimposed. It was therefore suggested that sometime approximating 4 or 5 days following injection was a crucial one as regards susceptibility differences.

Experiment 4 was carried out in an attempt to obtain a series of these curves in the same animal at different intervals during which the curves would be unlike. Dog 40–133, an adult, normal beagle, weighing 8.1 kg., was bled twice as the animals above and, 5 hours after the second bleeding of 200 ml., a single dose of 31 mg. of radio-

active iron was given by vein. Twelve hours after the injection, blood was withdrawn for study. Another bleeding was carried out at 36 hours, a third at 84 hours, and one at 6½ days. The progressive approach of the curve for hemolysis of the tagged cells toward that for the whole mass of circulating cells can be seen in Chart 2.

**Discussion.** When the dogs employed for these studies have been anemic for long periods due to chronic hemorrhage, the mean age of the cells in the circulation will probably only be about several weeks. The exact age of the mean will be dependent upon the rate of replacement of the circulating cells by regeneration, and this in turn will be related to the diet and iron intake. Where normal dogs are employed, the average of the circulating red cells would be approximately one-half of the life span of the red cell, or probably over 60 days.[15]

It has been shown in a previous publication[13] that when a single dose of iron containing the radioactive isotope is fed an anemic dog, the concentration of the radioactive hemoglobin in the circulation increases progressively for from 3 to 7 days. Therefore, it cannot be concluded that cells are 5 days old merely because this amount of time has elapsed since injection of the isotope. Rather, the mean age of the cells would be more likely to approach the order of 3 days, 7 days after administration.

Since red cells were actively being formed with the utilization of the radio-iron at a time interval of 4 or 5 days, and since the difference in hypotonic susceptibility between new-formed cells and older ones became negligible 5 or 6 days after administration of radio-iron, it would seem that only the very young red cells (less than 4 days of age) were less resistant to saline.

It seems worth noting that the resistance of the very old tagged cells (130 days of age) of Dog 38–137 was possibly a little greater than the other cells of the circulation. The latter would probably differ in age from the tagged cells by only a matter of several weeks, since when the isotope was administered this animal was iron depleted and anemic. Therefore, a gradually decreasing susceptibility toward the end of the life span of the red cell might not be seen in such marked contrast here as in the other experiments where the age of the cells differed more widely.

When more active iron becomes available, or measurement sensitivity is increased, it may become possible to extend these studies considerably. At present, it is possible only to study a small portion of the hemolysis curves in a single experiment because of the necessity of using large amounts of blood in order to obtain accurate activity measurements.

**Summary.** When radioactive iron is administered in a single dose to a dog in which there is a stimulus for hemoglobin formation, the isotope is promptly incorporated into the pigment in the red cell. These cells (identified by their radioactivity) can be regarded as

of known age and then be compared with those of the general run of the cells of the circulation as concerns susceptibility to hypotonic saline.

The very new cells in the circulation are found to be markedly less resistant to the hypotonic salt solution than are the other older cells. This difference in susceptibility disappears after a period of about 3 or 4 days.

There is an indication that possibly the very old red cells (130 days) are more resistant to hypotonic saline than the circulating cells of the mean age group.

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## ERYTHROCYTE FRAGILITY CHANGES PRODUCED BY SULFANILAMIDE.

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Splenic enlargement after the administration of sulfanilamide has been previously described.[3,5–7] In an earlier communication concerning the pathology of the spleen[6] it was stated by one of us (W. A.): "The histologic appearance of the spleen was very suggestive of active hyperemia. Because of this it was proposed to test the fragility of the red blood cells to see if there was any deviation from the normal, and also to search for any other detectable

modification of the red blood cells." Since active splenic hyperemia is characteristic of hemolytic anemias, the fragility of the erythrocyte was stressed in the present study.

**Method.** The resistance of red blood cells to hemolysis by hypotonic saline solution was determined weekly in 15 rats receiving 1 gm./kg. sulfanilamide daily by stomach tube and in 5 control rats. These fragility tests were made using blood obtained by cutting the tail tip. Tubes were set up containing saline solution increasing in steps of 0.02% from 0.28 to 0.50% concentration. The readings were made after 1 hour at room temperature and again after 18 hours' incubation at 37°C. The highest saline concentration at which hemolysis was discernible was recorded in this investigation.

At the end of the second week, 2 untreated control and 3 sulfanilamide animals were sacrificed by decapitation and thereafter 1 control and 4 sulfanilamide animals were killed at approximately weekly intervals for a period of another month. The erythrocyte, leukocyte, reticulocyte and differential white blood cells counts were performed and hemoglobin (Sahli) content was determined. The spleens were removed and weighed. Routine gross and microscopic examinations were made on all organs.

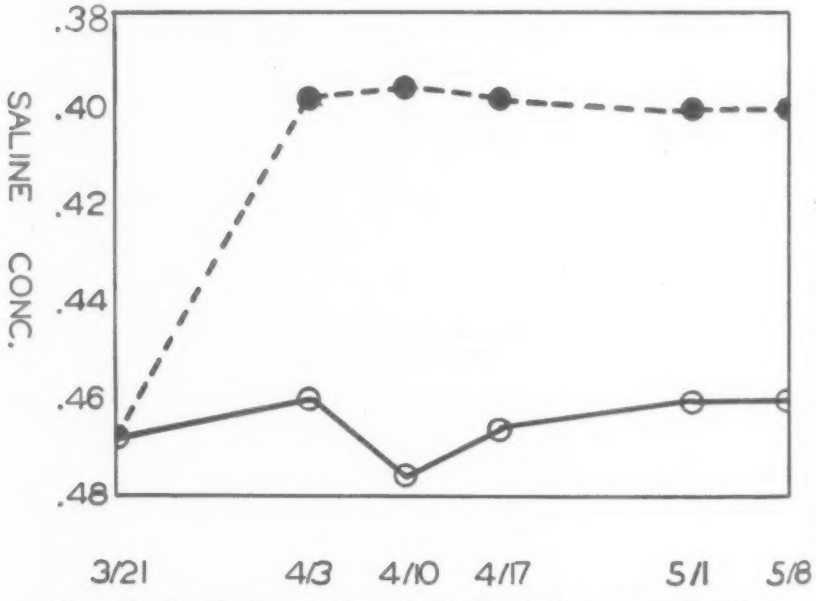


CHART 1.—Fragility changes after sulfanilamide administration. (●) Sulfanilamide treated rats. (○) Control (untreated) rats. Ordinate—saline concentration. Abscissa—date of fragility determination.

The average saline concentration for beginning hemolysis is shown in Chart 1. It was found that the resistance of the red blood cells to beginning hemolysis of the control rats remained essentially constant, initial hemolysis occurring in 0.46 to 0.48% saline. After 2 weeks of sulfanilamide administration (this being the first time

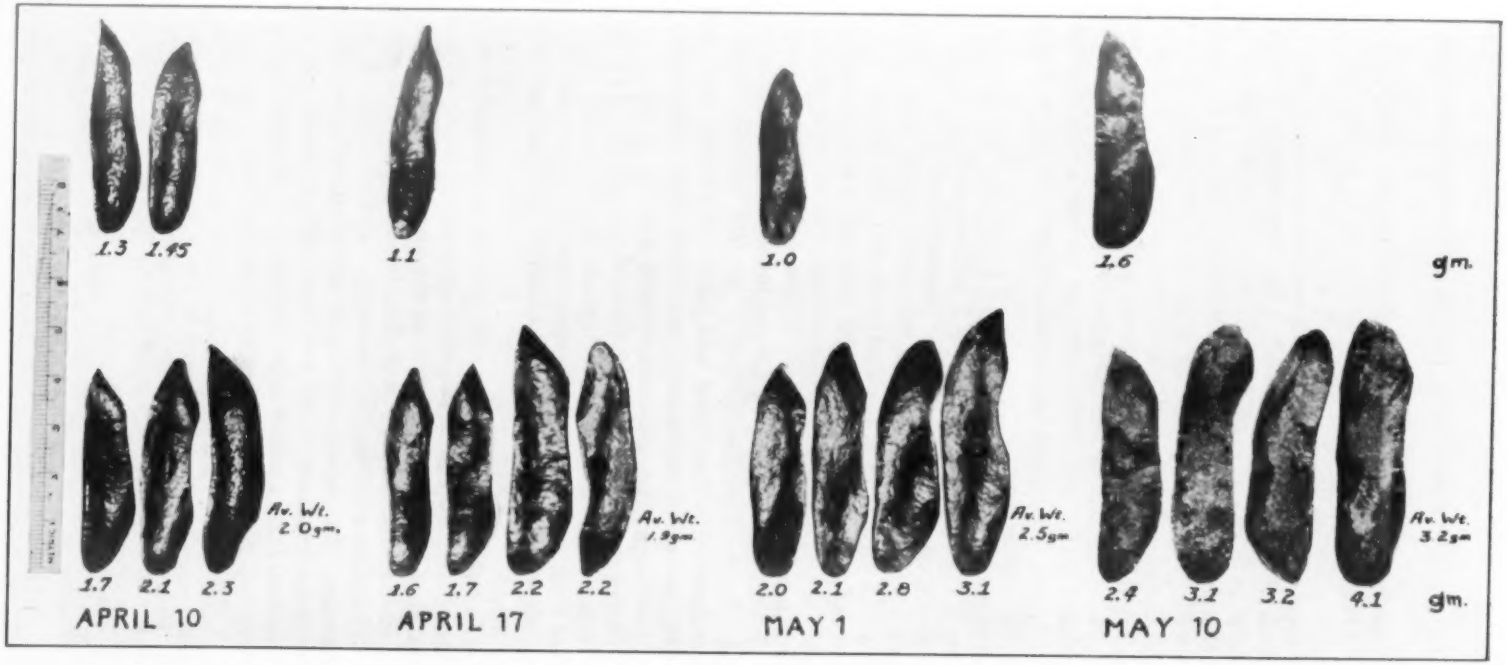


FIG. 1.—Splenomegaly in sulfanilamide rats. Upper row, control spleens; lower row, spleens from rats fed with sulfanilamide.

it was determined after instituting sulfanilamide), hemolysis of the red cells began at about 0.40. (In another series of rats, this change was already found to occur 18 hours after the first intraperitoneal injection of 2 gm./kg.) This value remained constant throughout the remainder of the experiment. The hemoglobin, erythrocyte, leukocyte and reticulocyte findings are in accord with those of Machella and Higgins.[5] The control animals showed an average of 7,900,000 erythrocytes per c.mm. as the final readings. The treated rats, on the other hand, developed a progressive anemia with a final average count of 3,900,000 erythrocytes per c.mm. The average final leukocyte count in the former group was 9600 per c.mm., and in the treated rats 11,800. The average normal reticulocyte counts were 1.35 per 1000 erythrocytes as compared with an average of 7.5 in the treated rats.

The control spleens varied in weight from 1.0 to 1.6 gm. (average 1.29 gm.). The splenic weights of 7 sulfanilamide-treated animals in the first 4 weeks of the experiment varied from 1.6 to 2.3 (average 1.94 gm.). The 4 spleens in the 6th week varied from 2.0 to 3.1 (average 2.5 gm.), and in the final week they varied from 2.4 to 4.1 (average of 3.2 gm.) (Fig. 1). The enlarged spleens were firm and showed a deep purple or even black color. Microscopic examination showed an active hyperemia such as seen in hemolytic anemia, and, in addition, an exaggerated hemosiderosis which was most pronounced in the perifollicular region, so that an iron stain of the section revealed a blue ring completely encircling each follicle. The livers were often enlarged. Frequently there was considerable loss of hair leaving extensive areas of alopecia.

The findings of changes in fragility of the red blood cells would be in accord with the increased urinary porphyrins in rats[9,10] and humans,[9] the increased urobilinogen excretions in humans,[2] and the anemia[1,3,5,8,10] and reticulocytosis[5] which has been reported after sulfanilamide.

The fact that the red blood cells showed an increased resistance to hemolysis by hypotonic saline solution is still in accord with the concept that the pathologic state of the erythrocyte is the primary factor in hemolytic anemia, and that the spleen plays a secondary rôle. (For literature, see Klemperer.[4])

**Summary.** The administration of sulfanilamide to rats results in an increased resistance of the red blood cells to hemolysis in hypotonic saline solution, and in splenomegaly with the histologic picture of active hyperemia such as seen in hemolytic anemia.

Since completing this manuscript Richardson (J. Pharm. and Exp. Ther., **70**, 370, 1940) reported the fragility changes in 3 mice fed 2% sulphanilamide for 2 weeks. He found that the blood in the sulphanilamide treated rats showed greater hemolysis in saline concentrations to 0.39%, but beyond this point the erythrocytes were more resistant.

We wish to express our appreciation to Miss Sally Woodford for her excellent technical assistance.

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## PERNICIOUS ANEMIA COMPLICATED BY MYELOGENOUS LEUKEMIA.

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The term leukanemia has long been used to describe an ill-defined syndrome of macrocytic anemia and leukemia, and even today appears at times as a special heading in the Quarterly Cumulative Index. In view of the recent advances in our knowledge of pernicious anemia as a deficiency disease, it seemed of interest to reëxamine the cases of leukanemia in the literature, and to report a case of myelogenous leukemia complicating well-established pernicious anemia.

Since 1900, when Leube[8] first described what he felt was a new disease entity, numerous cases of so-called leukanemia have been reported, chiefly in the German literature. Sinek and Kohn[15] reviewed the reported cases up until 1930 and rejected all of them except the one described by von Reichel.[12] In reëxamining the latter's report, however, the diagnosis of pernicious anemia is not conclusive. Likewise the cases of Elman and Marshall[5] and Barns and Rosenheim[1] fail to fulfill the requirements of a combined diagnosis. Most authors (Naegeli[11] and Muller and Werthemann[9]) do not agree with Jacobsohn[7] that the concept of leukanemia warrants a definite disease entity.

Well-substantiated cases of coëxisting chronic leukemia and an erythrocyte maturation factor deficiency anemia have been described by Rich and Schiff,[13] Touw and Graafland[18] and Doan.[4] To these we wish to add the following case report in which the

diagnosis of true Addisonian anemia terminating in myelogenous leukemia is justified.

**Case Report.** E. A. (No. 54059), a 57-year-old white married housewife, entered the Cincinnati General Hospital on March 28, 1936. She had been in perfect health until the fall of 1935 when she noted the onset of anorexia, weakness, and dyspnea. This became progressively worse until February, 1936, when it was exaggerated by nausea and vomiting.

Physical examination revealed a well-developed and obese woman despite evidence of considerable weight loss. The skin and mucous membranes were very pale. She had gray hair, blue eyes with an icteric tint to the scleræ, and several flame-shaped fresh retinal hemorrhages. The tongue was atrophic and there was moderate dependent edema. The liver, spleen and lymph nodes were not palpable. The neurologic examination was negative. The remainder of the physical examination disclosed no abnormalities.

The laboratory studies, disclosing a severe macrocytic anemia with leukopenia and the characteristic response to liver extract, are shown in Chart 1. The gastric analysis showed achlorhydria and a low total acid content by the alcohol-histamine method. Clinical improvement as well as hematologic response was noted.

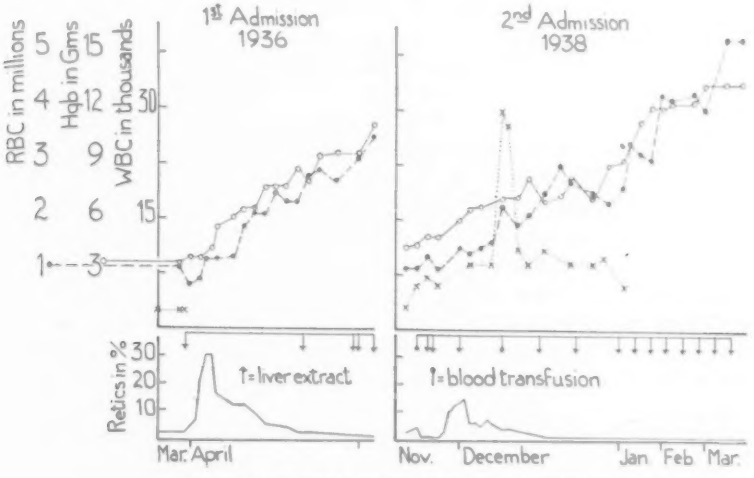


CHART 1.—Hematologic data of case reported.

After an interval of 2½ years, she reappeared at this hospital on Nov. 21, 1938, because of a relapse in her anemia, associated with cessation of specific treatment and the development of symptoms referable to the central and peripheral nervous systems.

The physical findings now were similar to those of the first admission plus the evidences of peripheral neuritis and dorso-lateral sclerosis of the spinal cord. The laboratory findings are seen in the second part of Chart 1. Sternal puncture revealed a megaloblastic bone marrow of the type characteristic of pernicious anemia. On this admission she was given a trial with an antianemic substance of undetermined potency, but on the fifth day, because of the appearance of a severe urinary tract infection, this was stopped and transfusions and potent liver extract given. By the middle of April, 1939, the blood picture was normal and great improvement was noted in her clinical condition.

Her third admission to this hospital was on Feb. 8, 1940, because of hemoptysis of 8 days' duration. Since April, 1939, she had substituted oral capsules for intramuscular liver. The physical examination revealed no cause for the hemoptysis. Roentgen rays of the chest were interpreted as indicating chronic bronchitis and bronchiectasis. The hematologic findings disclosed that the erythrocytes were 2.9 million, the hemoglobin 11 gm., the hematocrit 30, and the mean corpuscular volume 103. The leukocytes were 18,700 with neutrophils 75%, lymphocytes 21%, monocytes 3%, eosinophils 1%. It was noted that one-third of the neutrophils were "young forms." The platelet count was 406,000, the bleeding time 3 minutes, and the clotting time 2 minutes. She remained in the hospital 5 days and no hemoptysis occurred.

The fourth and final admission occurred on Sept. 18, 1940, $4\frac{1}{2}$ years after her first admission, when she entered the hospital in coma and died 45 minutes later. In the 7 months' interval between her last two admissions she was fairly well. She did her own housework, but was limited in it by weakness and dyspnea, which was not improved by liver injections or later by oral capsules given by her private physician. On Sept. 15, 1940, she suddenly developed diarrhea which continued for 3 days until she lapsed into coma 6 hours before arrival at the hospital.

When admitted to the hospital she was in deep coma. The temperature was 101°, the pulse undeterminable, the respirations 40. The abdomen was distended and the liver and spleen were not palpable. Emergency stimulants were administered in vain. Postmortem blood studies (heart's blood) showed the erythrocytes to be 2.6 million, hemoglobin 11.8 gm., leukocytes 100,000 with the following differential: myeloblasts, 3%; myelocytes A, 2%; myelocytes B, 16%; myelocytes C, 31%; metamyelocytes, 5%; stab forms, 16%; neutrophils, 18%; lymphocytes, 2%; basophils, 3%; and basophilic myelocytes, 1%.

*Autopsy* (5 hours postmortem, by Dr. H. Shanes): The *spleen* was markedly enlarged (1075 gm.), soft, friable, and a deep purplish-red with a definite grayish cast. The Malpighian corpuscles were not prominent. The *liver* was also markedly enlarged (1085 gm.). It was soft, friable, and with no gross evidence of necrosis or infiltration. The *lymph nodes* were grossly normal. Sections of the *bone marrow* taken from the body of the sternum, ribs, and lumbar vertebræ were all similar grossly, and presented a porous sponge-like appearance, with a homogeneous dull grayish-yellow color.

Microscopically, there was evidence of chronic myeloid leukemia with infiltration of the leukemic cells into the spleen, liver, lung, uterus, and submucosal layer of the stomach. Giemsa stains of several sections of bone marrow revealed young cells of the myeloid series completely filling the marrow. Of some interest was the absence of pronounced leukemic infiltration in the lymph nodes and kidney. There was also evidence of posterior (and suggestive lateral) column demyelinization of the spinal cord. In addition, there was demonstrated acute ulcerative typhlitis and chronic active pyelonephritis.

**Discussion.** We think that there is little doubt that this case represents pernicious anemia complicated by subacute myelogenous leukemia. There may be many sources of error in attempting to make a combined diagnosis. Numerous authors (Sturgis and Isaacs,[17] Castle and Minot,[3] Sharp *et al.*[14] and Heck,[6]) have shown that in cases of pernicious anemia in relapse, especially when the red count is low, a small number of myelocytes, and even an occasional myeloblast, may appear in the peripheral blood, and that

during remission a left shift in the neutrophils occurs with the occasional appearance of a few younger forms in this series. We likewise have noted in our own cases of pernicious anemia similar abnormalities. A bone marrow examination and the subsequent course of the patient after therapy, with a rise in the red count and a disappearance of the neutropenia, is sufficient evidence to indicate a so-called myeloid reaction in pernicious anemia. A persistent neutropenia despite adequate treatment should raise the question of a subleukemic leukemia.

Just as pernicious anemia may for a time simulate leukemia hematologically, so may leukemia simulate pernicious anemia. It is well known that while the associated myelophthisic anemia is most often normocytic, it may frequently be macrocytic. This, plus the usual leukopenia (in subleukemic states) and the thrombocytopenia, may suggest pernicious anemia. If the differential leukocyte count is carefully examined, pathologic cells will almost always be found in cases of leukemia, and more particularly bone marrow biopsy should reveal definite evidence of leukemia.

One can only speculate concerning these two diseases in the same patient, for although the most reasonable explanation is that of coincidence, it might be supposed that improperly treated pernicious anemia eventually predisposes the marrow to leukemic changes. The extreme rarity of this combination, despite the frequency of inadequately treated pernicious anemia, makes this most unlikely. Murphy,[10] who has seen a great number of cases of pernicious anemia, does not even mention the possibility of leukemia in his discussion of the complications of the disease. A third, but for similar reasons equally tenuous hypothesis, is that there is a fundamental defect, possibly hereditary, of the blood-forming organs, which makes the individual susceptible to either or both diseases. Along this line there are several reports in the literature describing leukemia and pernicious anemia or a pernicious anemia-like disease in siblings (Strandell,[16] and Bichel[2]). Until further evidence is available concerning the fundamental defect in leukemia, one must fall back upon chance as the most likely explanation of its association with pernicious anemia.

**Summary and Conclusions.** 1. The cases of leukanemia in the literature are reviewed and most of them rejected as failing to fulfill the requisites for the diagnosis of both pernicious anemia and leukemia.

2. The authors' own case is reported as a true Addisonian anemia terminating in myelogenous leukemia.

3. Pernicious anemia and subleukemic leukemia may for a time simulate each other. The difficulties in making a combined diagnosis are discussed.

4. The most satisfactory explanation for the occurrence of these two diseases in the same patient is that of coincidence.

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## HEMATOLOGIC CHANGES FOLLOWING SPLENECTOMY IN MAN, WITH PARTICULAR REFERENCE TO TARGET CELLS, HEMOLYTIC INDEX AND LYSOLECITHIN.*

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The dramatic results which often attend splenectomy in cases of hemolytic anemia and thrombocytopenic purpura have led us to detailed study of the splenectomized individual as a means of attaining knowledge of splenic function. The present publication deals with the study of 19 individuals who were splenectomized for various conditions and who were carefully studied at various intervals. In particular, modern hematologic methods were utilized with especial reference to "target" cells, hypotonic fragility, blood platelets, the question of blood destruction, and the "lysolecithin" metabolism. From these studies evidence was obtained in support of the concept that one or more splenic hormones exist, as well as confirmation of the frequently expressed view that the spleen aids in blood destruction.

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**Material.** Investigations were performed in 8 normal individuals and in 19 patients splenectomized for various causes from 4 weeks to 15 years previous to our studies. The splenectomized material may be divided into two groups: (1) *non-hemolytic*, 11 cases; traumatic rupture, 2; "Banti's" disease, 1; Gaucher's disease, 1; lymphatic leukemia, 1; and idiopathic thrombocytopenic purpura, 6. (2) *hemolytic*, congenital type, 4; acquired type, 4. This grouping was thought advisable because the cases with increased hemolysis showed marked changes in the shape of erythrocytes as well as greatly increased blood destruction preoperatively, differentiating them sharply from the non-hemolytic group.

**Methods.** A. Hematologic Methods. *Hemoglobin:* Evelyn or Cenco photoelectric method (100% = 15.5 gm. per 100 cc. of blood).

*Red cell count; white cell count:* U. S. Bureau of Standards certified pipettes and hemocytometers used; automatic shaker.

*Platelet count:* Method of Dameshek.[9a] Normal count, 400,000 to 900,000 per c.mm.

*Reticulocyte count:* Both "dry" and "wet" methods used. In the "wet" method, the technique of Dameshek[9a] was used.

*Hematocrit:* Venous blood collected in 5-cc. vials containing dry ammonium oxalate 6 mg., and potassium oxalate 4 mg. Centrifugation in Wintrobe type hematocrit tubes for 25 minutes at 3500 r.p.m.

*Mean corpuscular volume:* Normal range 84 to 94 cu. micra.

*Mean corpuscular diameter:* Price-Jones curves obtained by counting diameters of 200 cells using calibrated micrometer eye-piece. Normal mean diameter 7.4 to 7.6 micra.

*Mean corpuscular thickness:* $\pi\left(\frac{\text{M.C.V.}}{\text{Diameter}}\right)^2$. Normal thickness 1.9 to 2.2 micra.

*Howell-Jolly bodies:* Expressed in per cent of 100 red blood cells from Wright's stained films. Normally none present.

*Target cells:* Expressed in per cent of 100 red blood cells from stained films, in which these cells have the appearance of a "bull's eye" or target. In fresh preparations of blood, they are thin and highly flexible, assuming cup and bowl shapes. Normally less than 1% are present.

*Fragility of the red cells to hypotonic solutions of sodium chloride:* Method of Daland and Worthley.[8] Normal values: Hemolysis begins at 0.46% to 0.44%; complete at 0.26% to 0.24%.

*Bone-marrow biopsy:* Sternal puncture method used.

B. Methods Used in the Interpretation of Erythrocyte Destruction. *Bilirubin:* Qualitative methods of van den Bergh. Quantitative method of Malloy and Evelyn;[25] Evelyn or Cenco photoelectric colorimeter used. Normal 0.3 to 1 mg. per 100 cc.

*Urobilinogen in feces:* Quantitative determination. Method of Watson,[33a] based on the original method of Terwen[32] and the modification of Fuerth and Singer.[11] Normal level of urobilinogen excretion 40 to 200 mg. per day (average of 4-day collection of feces).

*Hemolytic index:* $\frac{\text{Urobilinogen output per day}}{\text{Total hemoglobin in gm.}} \times 100$. This index (first proposed by Belanogowa[4]) expresses the urobilinogen excretion per day in relationship to 100 gm. of hemoglobin. Normal value 11 to 21 mg. per 100 gm. of hemoglobin. The total hemoglobin is computed from the hemoglobin content in grams per 100 cc. of blood and from the total blood

volume. The advantage of the hemolytic index is that it takes into account the fluctuations which occur in urobilinogen output with variations in the total mass of hemoglobin in the body.

*Blood volume:* Method of Gibson and Evans,[12] using the Evans blue dye, and the Evelyn photoelectric colorimeter (micro attachment).

C. Lysolecithin. *Determination of lysolecithin content of blood:* Method of Singer;[31b] the hemolytic titer of a serum extract containing this lysin is determined.

*Lysolecithin "quotient":* The lysolecithin titer of unincubated serum is compared to that of an aliquot sample of incubated unmoved serum. Singer[31c] has shown that the lysolecithin titer of normal serum (1:2 to 1:8 in man) is increased two to eight-fold by incubating the serum for several hours. This increase, which is apparently due to the action of an enzyme normally present in plasma is expressed in the lysolecithin quotient:

$$\frac{\text{Lysolecithin content of unincubated serum}}{\text{Lysolecithin content of incubated serum}} = \text{LLQ}$$

Normally this quotient in circulating blood is a fraction of 1, *i. e.*, $\frac{1}{2}$ to $\frac{1}{8}$.

Table 1.—Normal Cases.

| Case. | Sex. | Age. | Hb., gm. | Hb., % | Daily fecal urobilinogen, mg. | Hemolytic index. | Expected blood volumes, in cc.* | | | Determined blood volume, in cc. | | | Total circulating Hb., gm. | Lysolecithin content. | | Lysolecithin quotient. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | R.B.C. | Plasma. | Total. | R.B.C. | Plasma. | Total. | | Unincubated. | Incubated. | |
| 1 | M | 32 | 15.0 | 97 | 66.2 | 11.1 | 1977 | 2193 | 4170 | 1914 | 2074 | 3988 | 598 | 1:2 | 1:8 | 1:4 |
| 2 | F | 40 | 14.7 | 95 | 75.0 | 11.2 | 1763 | 2337 | 4100 | 1994 | 2540 | 4534 | 667 | 1:8 | 1:16 | 1:2 |
| 3 | M | 25 | 15.6 | 100 | 85.6 | 11.4 | 2475 | 3025 | 5500 | 2280 | 2520 | 4800 | 749 | 1:4 | 1:32 | 1:8 |
| 4 | M | 63 | 14.6 | 94 | 86.5 | 12.3 | 2295 | 2805 | 5100 | 1966 | 2830 | 4796 | 700 | 1:4 | 1:16 | 1:4 |
| 5 | F | 64 | 13.9 | 90 | 68.0 | 13.3 | 1484 | 1966 | 3430 | 1222 | 1733 | 2955 | 511 | 1:4 | 1:8 | 1:2 |
| 6 | M | 25 | 17.2 | 111 | 180.0 | 19.2 | 2637 | 3223 | 5860 | 2660 | 2770 | 5430 | 934 | 1:2 | 1:8 | 1:4 |
| 7 | F | 38 | 13.3 | 86 | 92.1 | 20.3 | 1527 | 2023 | 3550 | 1275 | 2125 | 3400 | 452 | 1:4 | 1:16 | 1:4 |
| 8 | M | ... | 13.2 | 85 | 105.5 | 20.8 | 2070 | 2530 | 4600 | 2051 | 2558 | 4609 | 508 | 1:4 | 1:16 | 1:4 |

* Expected blood volumes based on the surface areas of the patients.

**Results** (Tables 1 and 2). 1. *Hemoglobin:* Although in most instances there was a slight reduction in hemoglobin values, in only 4 of the 9 cases was there definite anemia (below 12.5 gm.—80%). These were Cases 1 (atypical leukemia), 3 (Gaucher's disease), 8 (hepatic cirrhosis) and 15 (continuing or relapsed hemolytic anemia).

2. *Red blood cell count:* Of the 19 splenectomized patients, 3 (Cases 8, 15, and 18) showed red cell counts below 4 million per c.mm. In these cases, particularly in Case 15, the anemia was in all probability caused by continuation of the underlying pathologic process. Thus there were no cases in which anemia clearly related to splenectomy *per se* was present.

3. *Leukocytes* (Table 3): The white cell count was definitely elevated (above 12,000) in one-half the cases and above 10,000 in 12 of 19. However, in Case 1, chronic lymphatic leukemia was present several years after splenectomy for "Banti's disease," and

TABLE 2.—SPLENECTOMIZED CASES.

| Groups considered under "Results." | | | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | | | | 9 | 10 | 11 | | | | | | | 12 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case. | Sex. | Age. | Diagnosis. | Time after splenectomy. | Hb., gm. | Hb., %. | R.B.C., millions per c.mm. | W.B.C., thousands per c.mm. | Platelets, thousands per c.mm. | Reticulocytes, %. | Howell-Jolly bodies, %. | Target cells, %. | Hypotonic fragility, % NaCl solution. | | M.C.V.,* cu. micra. | M.C.D.,* micra. | M.C.T.,* micra. | Serum bilirubin, mg. per 100 cc. | Fecal urobilinogen, daily output, mg. | Hemolytic index, mg. per 100 gm. of Hb. | ‡ Expected blood volumes, in cc. | | | Determined blood volumes, in cc. | | | Total circulating Hb., gm. | Lysolecithin content. | | Lysolecithin quotient. |
| | | | | | | | | | | | | Begins. | Complete. | | | | | | | R.B.C. | Plasma. | Total. | R.B.C. | Plasma. | Total. | | Uninculated. | Incubated. | |
| | | | | | | | | | | | | GROUP I. NON-HEMOLYTIC | | | | | | | | | | | | | | | | |
| 1 | M | 15 | Lymphatic leukemia | 8 yrs. | 12.0 | 77 | 5.4 | 17.8 | 663 | 1.4 | 0.3 | 20.0 | 40 | .08 | 83.3 | 7.6 | 1.84 | 0.38 | 17.6 | 3.6 | 1971 | 2409 | 4380 | 1781 | 2342 | 4123 | 495 | 1:1 | 1:4 | 1:4 |
| 2 | M | 24 | Traumatic rupture | 9 mos. | 14.9 | 96 | 4.9 | 10.6 | 2055 | 0.8 | 0.4 | 9.6 | 40 | .08 | 98.1 | 7.3 | 2.34 | 0.68 | 55.0 | 8.0 | 2520 | 3080 | 5600 | 2556 | 2770 | 5326 | 794 | 1:2 | 1:8 | 1:4 |
| 3 | M | 10 | Gaucher's disease | 20 mos. | 10.3 | 66 | 4.2 | 18.3 | 952 | 2.0 | 0.3 | 2.4 | 44 | .16 | 85.1 | 8.0 | 1.69 | 0.37 | 29.4 | 14.6 | 936 | 1144 | 2080 | 695 | 1263 | 1958 | 202 | 1:4 | 1:4 | 1:1 |
| 4 | F | 35 | Purpura | 18 mos. | 14.3 | 92 | 4.9 | 15.5 | 626 | 1.4 | 0.7 | 2.7 | 42 | .12 | 87.2 | 7.2 | 2.14 | 0.77 | 37.5 | 6.5 | 1711 | 2269 | 3980 | 1703 | 2258 | 3961 | 566 | 1:1 | 1:4 | 1:4 |
| 5 | F | 50 | Purpura | 3 yrs. | 13.4 | 86 | 4.6 | 13.3 | 975 | 1.5 | 0.5 | 0.5 | 42 | .12 | 94.5 | 7.8 | 1.97 | 0.33 | 61.4 | 11.4† | 1733 | 2297 | 4030 | ... | ... | ... | 540† | ... | ... | ... |
| 6 | F | 18 | Purpura | 3 yrs. | 14.2 | 91 | 4.6 | 6.1 | 666 | 0.5 | 2.2 | 3.4 | 44 | .12 | 93.6 | 7.2 | 2.30 | 0.37 | 45.8 | 6.1 | 1570 | 2080 | 3650 | 2270 | 3020 | 5290 | 750 | 1:1 | 1:4 | 1:4 |
| 7 | F | 38 | Purpura | 8 mos. | 14.7 | 95 | 4.9 | 15.6 | 1137 | 1.1 | 0.9 | 4.6 | 48 | .08 | 98.8 | 7.7 | 2.12 | 0.26 | 27.8 | 4.6† | 1763 | 2337 | 4100 | ... | ... | ... | 603† | 1:2 | 1:2 | 1:1 |
| 8 | F | 19 | Cirrhosis of liver | 13 mos. | 10.1 | 65 | 3.7 | 7.1 | 564 | 0.9 | 0.7 | 11.2 | 42 | .08 | 98.9 | 7.8 | 2.07 | 0.97 | 31.3 | 5.7 | 2365 | 3135 | 5500 | 2004 | 3413 | 5417 | 547 | 1:2 | 1:2 | 1:1 |
| 9 | M | 40 | Traumatic rupture | 15 yrs. | 15.9 | 102 | 5.3 | 7.7 | 807 | 0.8 | 1.3 | 0.2 | 46 | .20 | 91.2 | 7.5 | 2.07 | 0.50 | 72.9 | 8.9 | 2412 | 2948 | 5360 | 2419 | 2728 | 5147 | 818 | 1:2 | 1:4 | 1:2 |
| 10 | M | 45 | Purpura | 7 wks. | 13.0 | 84 | 4.8 | 10.2 | 540 | 1.9 | 0.8 | 2.7 | 48 | .12 | 87.7 | 7.3 | 2.09 | 0.32 | 22.2 | 3.4 | 2295 | 2805 | 5100 | 1961 | 3029 | 4990 | 649 | 1:1 | 1:8 | 1:8 |
| 11 | F | 25 | Purpura | 4 wks. | 13.2 | 85 | 5.3 | 10.4 | 1045 | 2.2 | 0.4 | 2.4 | 40 | .12 | 84.2 | 7.6 | 1.86 | 0.30 | 25.2 | 5.6 | 1763 | 2337 | 4100 | 1442 | 1929 | 3371 | 445 | ... | ... | ... |
| | | | | | | | | | | | | GROUP II. HEMOLYTIC | | | | | | | | | | | | | | | | | |
| 12 | F | 36 | Acquired hemolytic anemia | 3 yrs. | 14.0 | 90 | 4.3 | 12.8 | 661 | 0.8 | 1.3 | 1.3 | 46 | .12 | 107.2 | 8.1 | 2.08 | 0.21 | 30.0 | 5.2† | 1763 | 2337 | 4100 | ... | ... | ... | 574† | 1:4 | 1:4 | 1:1 |
| 13 | M | 4 | Acquired hemolytic anemia | 3 yrs. | 13.0 | 84 | 4.3 | 9.4 | 524 | 1.6 | 0.3 | 2.4 | 42 | .16 | 90.4 | 7.1 | 2.28 | .... | 16.0 | 5.8† | 959 | 1171 | 2130 | ... | ... | ... | 279† | ... | ... | ... |
| 14 | F | 44 | Acquired hemolytic anemia | 1 yr. | 15.0 | 96 | 5.0 | 14.0 | 718 | 2.7 | 0.4 | 1.9 | 44 | 12 | 90.3 | 7.4 | 2.10 | 0.95 | 86.4 | 14.8 | 1733 | 2297 | 4030 | 1704 | 2169 | 3873 | 581 | 1:1 | 1:1 | 1:1 |
| 15 | F | 42 | Acquired hemolytic anemia | 9 yrs. | 8.8 | 57 | 2.5 | 19.5 | 1248 | 25.2 | 0.6 | 0.3 | 42 | 20 | 103.1 | 7.6 | 2.27 | 1.35 | 495.0 | 149.0 | 1570 | 2080 | 3650 | 943 | 2830 | 3773 | 332 | 1:1 | 1:1 | 1:1 |
| 16 | M | 14 | Congenital hemolytic anemia | 2 yrs. | 14.5 | 94 | 4.8 | 8.9 | 1061 | 1.4 | 0.5 | 0.2 | 56 | 12 | 90.0 | 6.3 | 2.88 | 0.88 | 58.3 | 7.5 | 2340 | 2860 | 5200 | 2231 | 3057 | 5288 | 767 | 1:4 | 1:4 | 1:1 |
| 17 | F | 10 | Congenital hemolytic anemia | 2 yrs. | 13.9 | 90 | 4.5 | 7.4 | 1472 | 3.7 | 0.1 | 0.0 | 64 | 22 | 85.2 | 6.1 | 2.91 | 1.07 | 30.3 | 10.5† | 898 | 1182 | 2080 | ... | ... | ... | 288 | ... | ... | ... |
| 18 | F | 38 | Congenital hemolytic anemia | 8 yrs. | 13.2 | 85 | 3.8 | 8.5 | 459 | 0.3 | 0.4 | 0.5 | 60 | 20 | 100.5 | 7.1 | 2.51 | 0.97 | 69.7 | 14.0 | 1729 | 2291 | 4020 | 1452 | 2320 | 3772 | 498 | ... | ... | ... |
| 19 | M | 13 | Congenital hemolytic anemia | 7 mos. | 15.9 | 102 | 5.3 | 12.4 | 621 | 0.8 | 0.6 | 0.0 | 48 | 16 | 83.6 | 7.1 | 2.11 | 0.90 | 38.5 | 7.2 | 1710 | 2090 | 3800 | 1449 | 1919 | 3366 | 535 | 1:2 | 1:2 | 1:1 |

* M.C.V. = mean corpuscular volume; M.C.D. = mean corpuscular diameter; M.C.T. = mean corpuscular thickness.
† The expected blood volume was used in the calculation of the hemolytic index and total circulating hemoglobin value.
‡ Expected blood volumes based on the surface areas of the patients.

in Case 15 there was persistent hemolytic anemia with secondary leukocytosis. That the leukocytosis was not a temporary phenomenon is attested by the fact that it was still present in several cases operated upon at least 3 years previously.

TABLE 3.—LEUKOCYTE AND DIFFERENTIAL COUNTS IN SPLENECTOMIZED CASES.

| Case. | W.B.C. (thousands) per c.mm.). | N. | L. | M. | E. | B. |
|---|---|---|---|---|---|---|
| 1 | 17.8 | 34 | 47 | 16 | 3 | 0 |
| 2 | 10.6 | 71 | 19 | 9 | 1 | 0 |
| 3 | 18.3 | 55 | 36 | 3 | 4 | 2 |
| 4 | 15.5 | 43 | 45 | 12 | 0 | 0 |
| 5 | 13.3 | 44 | 30 | 15 | 11 | 0 |
| 6 | 6.1 | 46 | 36 | 17 | 1 | 0 |
| 7 | 15.6 | 66 | 25 | 9 | 0 | 0 |
| 8 | 7.1 | 32 | 42 | 18 | 7 | 1 |
| 9 | 7.7 | 56 | 27 | 14 | 2 | 1 |
| 10 | 10.2 | 51 | 33 | 11 | 5 | 0 |
| 11 | 10.4 | 52 | 36 | 12 | 2 | 0 |
| 12 | 12.8 | 50 | 35 | 7 | 8 | 0 |
| 13 | 9.4 | 22 | 68 | 6 | 4 | 0 |
| 14 | 14.0 | 45 | 40 | 14 | 1 | 0 |
| 15 | 19.5 | 67 | 17 | 11 | 3 | 2 |
| 16 | 8.9 | 48 | 40 | 9 | 2 | 1 |
| 17 | 7.4 | 56 | 32 | 11 | 1 | 0 |
| 18 | 8.5 | 69 | 23 | 6 | 2 | 0 |
| 19 | 12.4 | 49 | 29 | 15 | 6 | 1 |

Despite the elevation in leukocyte count commonly present, the neutrophils usually showed a *relative* reduction in their number. Thus the percentage of neutrophils was less than 60 in 15 of the 19 cases. The absolute number of granulocytes was generally normal, although in several cases (Cases 6, 8, 9, 13, 17) an absolute reduction in granulocytes was present. Conversely, the lymphocytes and monocytes were generally increased in both a relative and absolute fashion. It is noteworthy that in 9 of the 19 cases, the monocyte percentage was 12% or over. Seven of the cases showed an eosinophilia of 4% or over.

4. *Platelets:* Eight of the 19 patients (Cases 2, 3, 5, 7, 11, 15, 16, 17) showed increased platelet counts (above 900,000 per c.mm.). The highest count (2,055,000) was observed in Case 2, operated upon 9 months previously because of traumatic rupture of the spleen. In 3 cases of thrombocytopenic purpura observed 4 weeks, 8 months and 2 years respectively after operation, the platelet counts were still abnormally high and the same finding was present in 2 cases of hemolytic anemia operated upon 2 years previously. There was no definite parallelism between elevations in the leukocyte and platelet counts, although some cases showed both.

5. *Reticulocytes:* The reticulocyte counts were generally within the normal range of 0.3% to 1%. In Case 3 (Gaucher's disease) the reticulocyte count was 2% and in Cases 14 and 17 (splenectomized for hemolytic jaundice) the reticulocytes numbered 2.7% and 3.7% respectively. Case 15, with severe hemolysis and sphero-

* M.C.V. = mean corpuscular volume; M.C.D. = mean corpuscular diameter; M.C.T. = mean corpuscular thickness.
† The expected blood volume was used in the calculation of the hemolytic index and total circulating hemoglobin value.
‡ Expected blood volumes based on the surface areas of the patients.

cytosis persisting 9 years after splenectomy, had 25.2% reticulocytes. Thus no effect upon the reticulocyte level by splenectomy *per se* was discovered.

6. *Howell-Jolly bodies:* These definitely pathologic erythrocytes were found in varying number in *all* the cases regardless of the time elapsed since operation. This finding was the most constant one encountered in our studies.

7. *Target cells:* These recently described[3] abnormal erythrocytes were present in increased numbers (above 1%) in 12 of the 19 cases (Cases 1 to 4, 6 to 8, 10 to 14). Although we have set an arbitrary level of 1% as the upper limit of normality, ordinarily very few target cells are found. All cases without persistent hemolytic anemia (with the exception of Cases 5 and 9) showed an increase of target cells. Of great interest were the contrasting findings after splenectomy between the cases of acquired and congenital hemolytic jaundice. In the congenital group (Cases 16 to 19) target cells were not increased, whereas in the acquired group, despite well-marked spherocytosis prior to splenectomy, target cells were definitely increased over normal. This finding was associated with a complete disappearance of the spherocytosis. There was no parallelism between the number of Howell-Jolly bodies and target cells. No nucleated red cells were found in the peripheral blood in our cases.

8. *Hypotonic fragility:* Haden[14] demonstrated the relationship which exists between the thickness of the erythrocyte and its hypotonic fragility. The thicker the red cell, the more fragile it is in hypotonic salt solution and *vice versa*. Following splenectomy in Cases 1 to 14 (showing normal or diminished hemolysis) the hypotonic fragility of the erythrocytes was decreased in almost every instance. The decreased saline fragility was more clearly expressed in the so-called "minimum fragility," *i. e.*, that solution which showed complete hemolysis. Whereas normally, complete hemolysis occurs in solutions 0.30% to 0.24% NaCl, after splenectomy complete hemolysis took place only in solutions 0.16% to 0.08% NaCl. There was a direct parallelism between the increase in minimum resistance and that of the relatively thin target cells. In cases of hemolytic anemia (Cases 15 to 19) with persistent spherocytosis, the maximum fragility remained *increased*, although the minimum fragility might be diminished.

*M.C.V., M.C.D., M.C.T.:* The mean corpuscular volume was in general little affected, most cases showing normal values (between 84 and 94 cu. micra), although a few showed borderline macrocytosis. Except in the congenital hemolytic group, the mean cell diameter was either normal or slightly increased. Cases 3, 5, 8 and 12 presented values of 8.0, 7.8, 7.8, and 8.1 respectively. Of these, Cases 3 (Gaucher's disease) and 8 (hepatic cirrhosis) showed definite evidence of liver disease in which macrocytosis is not uncommonly present. Case 12, with both an elevation in the mean

cell volume and diameter was an example of cured acquired hemolytic anemia. The mean cell thickness was within normal range (1.7 to 2.3 micra) in all the cases except those of the congenital group, in which it was increased.

8A. *Bone-marrow findings:* The bone-marrow was studied in several cases but sufficiently detailed changes to warrant any statement of results have thus far not been found.

9. *Bilirubin:* The bilirubin values of most of the cases were within normal limits. The congenital hemolytic cases tended to show persistent slight bilirubinemia even after splenectomy.

10. *Urobilinogen excretion in the feces; Hemolytic index:* The daily urobilinogen excretion expressed in absolute values was either normal (40 to 200 mg. per day, Cases, 2, 4, 5, 6, 9, 14, 16, 18, 19), or less than normal (Cases 1, 3, 7, 8, 10 to 13, 17). That a low absolute daily value for urobilinogen does not always indicate a diminution in the output of the pigment may be recognized from the hemolytic index. This was determined in 14 of the 19 cases and was found to be lowered (less than 11 mg.) in 10, *i. e.*, in about two-thirds of the cases. Only in Cases 3, 14, and 18 was the index normal and in Case 15 (chronic hemolytic anemia) it was increased. The normal or slightly increased index in these cases was probably adequately explained by consideration of the various underlying pathologic processes. Of particular interest was the fact that 3 of 4 cases splenectomized for congenital hemolytic jaundice, although continuing to show slight spherocytosis and an increased saline fragility, nevertheless presented a low hemolytic index. No definite parallelism between the number of target cells present and the low hemolytic index could be demonstrated, nor was there any relationship of the index to the time after operation. Thus, a low index was present in Case 9, operated upon 15 years previously for traumatic rupture of the spleen.

11. *Blood volume:* Determination of the hemolytic index, which involves measurement of the blood volume, gave us the opportunity to compare the actual blood volume with the expected blood volume as computed from the surface area. Relatively small deviations from the expected volumes were found, except in Case 6 in which a definite increase in volume was noted and in Case 11 where the blood volume was definitely decreased.

12. *The lysolecithin metabolism:* One of us[31b,c] has previously investigated the mechanism of the production of lysolecithin, a hemolytic substance which was discovered in normal blood serum by Bergenhem and Fåhraeus.[5] This mechanism can be expressed by the lysolecithin quotient. (L.L.Q.) Normally, in circulating blood (*i. e.*, blood in motion) this quotient is always a fraction of 1. In the reservoir blood of the spleen, which is at least temporarily excluded from the circulation and presumably acts like incubated unmoved blood, the LLQ was found to be 1. The spleen, which may be

termed the "incubator of the body," at least as regards lysolecithin and its action upon red blood cells, produces a material amount of lysolecithin which cannot be further increased by incubation.

Following splenectomy in 6 of 14 cases studied, the lysolecithin content of the unincubated serum from the peripheral blood was considerably lower than in normal individuals, a finding also obtained by Gripwall.[13] Normally, complete hemolysis of normal red cells occurs in dilutions of 1:2 to 1:16 of lysolecithin extracted from 10 cc. of serum. In the 6 cases above mentioned, complete hemolysis was observed only in dilutions of 1:1. In 8 of 14 cases examined, no increase of the lysolecithin content of the serum occurred after incubation, resulting in a LIQ of 1. Since there was no question of "reservoir blood" this suggests a disturbance in the mechanism of the production of lysolecithin following splenectomy.

13. *Animal experiments:* Additional experiments were carried out in 3 dogs, 8 guinea-pigs, and 1 rabbit, in all of which hematologic studies were made before and after splenectomy. In general, the results in these normal animals were identical with those found in the human cases. In the dogs, target cells became extremely prominent. Thus in Dog 1, the peak target cell count was 72%, 109 days after splenectomy; 162 days after operation, the target cell count had become stabilized at approximately 33%. There was no anemia at this time and the hypotonic fragility was definitely decreased (from control 0.56% to 0.26%, to 0.44% to 0.16%). Howell-Jolly bodies were also present and there was marked leukocytosis. In the guinea-pigs, the percentage of target cells approximated that found in the human (5% to 10%) with an associated diminution in hypotonic fragility, but the outstanding feature was the extreme thrombocytosis. In the rabbit, an extreme increase in platelets was also present, but even after 4 months, target cells were few in number and the hypotonic fragility was not increased.

**Discussion.** *Analysis of Results and Discussion of Literature.* The most important reviews dealing with the effects of splenectomy are those of Pearce, Krumbhaar, and Frazier[28] (1914); Krumbhaar[21] (1932); and Lauda[22] (1933). Our studies, which deal chiefly with the hematologic findings in a series of splenectomized humans, are in general confirmatory of previous findings and add a few details based on recently developed hematologic methods. In the review of Pearce, Krumbhaar and Frazier,[28] the effects of splenectomy in normal dogs are carefully studied. In the main, three results were noted: a varying degree of transient anemia, increased hypotonic resistance of the erythrocytes, and a diminished tendency for the development of jaundice when hemolytic agents were administered. Much emphasis is laid upon the anemia which was commonly present for several weeks. Krumbhaar's[21] review of 1932 again stresses the anemia, which at least indirectly is stated to be associated with the increase in red cell resistance. The monograph of Lauda[22] on the physiology

of the spleen is a carefully documented and critical review of all the knowledge of splenic physiology to 1933, together with a very complete bibliography. The final chapter is devoted to a discussion of evidence for and against the likelihood that internal secretions of the spleen exist.

1. *Hemoglobin and Red Cell Count.* No really definite anemia was present in our uncomplicated cases, which were studied at varying intervals (4 weeks to 15 years) after splenectomy. Although Krumbhaar[21] and a number of other investigators found anemia after removal of the normal spleen, it should be noted that this finding has frequently failed of confirmation; indeed, polycythemia has at times been noted. The contradictory results,* as Lauda[22] points out, are at least partly due to differences in animals, techniques, diets, the length of time that had elapsed after splenectomy and so on. At any rate, the anemia in the splenectomized dogs was transitory and probably without bearing on the question of red cell resistance, Howell-Jolly bodies, and so on. This is shown by the presence of these abnormalities in our cases, although anemia was absent.

2. *Leukocytes.* A persistent leukocytosis which was present in one-half our cases was due chiefly to an absolute increase in lymphocytes, monocytes, and to a lesser extent in eosinophils. The reasons for these findings are not clear, although they have repeatedly been noted (*cf.* Naegeli[26]).

3. *Platelets.* Thrombocytosis was present in many of the cases. The striking increases in platelets which follow splenectomy have been known for many years. Our studies in thrombocytopenic purpura have led us to conclude that the spleen normally exhibits an inhibitory effect upon platelet production in the bone-marrow. When this effect is removed, platelet production becomes greatly increased.

4. *Changes in the Red Cells.* (*a*) The most constant hematologic finding in our splenectomized material was the presence of Howell-Jolly bodies, first described by Hirschfeld and Weinert[18,19] and confirmed since in many investigations. The Howell-Jolly body appears to be a nuclear fragment in an otherwise fully mature erythrocyte. Although there is still some discussion as to the method of nuclear removal from the most mature normoblast, most authorities are in accord in believing that the nucleus is extruded *en masse* rather than by fragmentation. If this is correct, the presence of Howell-Jolly bodies would indicate, as pointed out by Hirschfeld and Weinert,[18,19] an abnormality in nuclear extrusion, and their

* The increase in the red cell count that some authors have observed after splenectomy is sometimes best explained on the basis of removal of a diseased spleen in the presence of an existing anemia. While there is not much evidence for removal of a normal spleen causing polycythemia (other than that of brief postoperative change in cell concentration), this procedure does not appear to cause either marked or lasting anemia.—EDITOR.

appearance after splenectomy, a control of this function by the spleen. This theory, which was the first to express a possible hormonal regulation by the spleen of a bone-marrow function, was apparently substantiated by the experiments of Lauda and Flaum.[23] These authors regularly observed Howell-Jolly bodies in splenectomized rats. When 2 rats were joined in parabiosis and the spleen of one of the partners removed, no Howell-Jolly bodies were observed. However, when the second partner was also splenectomized the blood of both showed erythrocytes with Howell-Jolly bodies. Erythrocytes containing these abnormal nuclear fragments are occasionally seen in conditions other than following splenectomy. Thus, Ching and Diggs[7] found these cells in certain cases of sickle cell anemia, and they have been observed in other conditions.

(*b*) *Target Cells and Increased Resistance of the Red Cells to Hypotonic Solutions.* The cause of the increased hypotonic resistance of the red cells after splenectomy has occasioned a great deal of speculation. Bottazzi,[6] who first observed this phenomenon in 1894, considered three possibilities: (1) anemia; (2) the presence of more resistant red cells arising from a rapidly growing bone-marrow; (3) the presence in the spleen of a special function to weaken certain red cells. Of these possibilities, he considered the third the most likely and accordingly postulated for the spleen a "hemacatatonistic" function. Pearce, Krumbhaar, and Frazier[28] believed that the increased resistance was probably associated with the anemia; the increased resistance in cases without anemia or after the anemia had disappeared was not adequately explained. Banti[1] and others postulated that the spleen possessed a hemolyzing function, and a number of workers have observed that red cells from the splenic vein were definitely more fragile than those from the splenic artery. In recent years, the work of Bergenhem and Fåhraeus[5] pointed to the possibility that the activity of "lysolecithin" in the relatively stagnant blood of the spleen might increase erythrocyte fragility. Ham and Castle[15] have recently concluded that the spleen is the chief "stasis" organ of the body and that there, as the result of at first purely physical and later of metabolic changes, the red cells became spheroidal and thus more readily destructible. Knisely's[20a,b] histologic studies in the living animal have beautifully demonstrated that blood, free of plasma, stagnates in splenic sinusoids for several minutes to several hours. Thus numerous studies bearing directly or indirectly on the problem, indicate that the red blood cells become modified in their passage through the spleen and that the modification is in the direction of increased spheroidicity and increased hypotonic fragility.

A definite morphologic basis for the increased hypotonic resistance of the erythrocytes after splenectomy has only recently been established. Barrett[3] noted the presence of "bull's eye" or "target types" of red blood cells in many cases of obstructive jaundice.

Because increased resistance of the red cells was simultaneously present, the possibility that these two abnormalities were related was suspected and careful studies brought out clearly that the more resistant red cells were indeed the target cells. Barrett[3] found that these cells were present chiefly in four groups of cases: (1) obstructive jaundice; (2) hypochromic anemia; (3) following splenectomy, and (4) in steatorrhea. His studies indicated that the target cell was thinner than the normal red cell and thus could imbibe more water before bursting (hemolyzing) in hypotonic solutions of salt. Thus, the target cell with *decreased* hypotonic fragility may be said to be the antithesis of the small, thick spherocyte of hemolytic jaundice with *increased* hypotonic fragility.

Following splenectomy in acute hemolytic anemia (hemolytic icterus of the *acquired* variety) it was noted that when the patient recovered, the hypotonic *resistance* of the red cells was increased and target cells were present. However, the splenectomized cases of congenital hemolytic jaundice, whether in crisis or otherwise, continued to show an increase in hypotonic *fragility* of the erythrocytes and target cells were absent. This has already been noted by Heilmeyer[16] and Dameshek and Schwartz[10] as an additional differential feature between the congenital and acquired cases of hemolytic jaundice.

It seems likely therefore that in the absence of the spleen, the red cell population tends on the whole to be thinner than normal. Although the red cells vary slightly in degrees of thickness, as in diameter, cells thin enough to be called "target cells" are few. With the spleen removed, there is probably a shift to a thinner population with a definite proportion (3% to 20%) of the erythrocytes becoming thin enough to be recognized as target cells. A definite and striking reduction in mean corpuscular thickness in our cases was not observed, although in general a tendency to diminished values was present. In congenital hemolytic jaundice, with thick cells being persistently formed, the reversion to somewhat diminished thinness after splenectomy is not sufficient to result in the appearance of target cells, as in the acquired cases. The probable reduction in erythrocyte thickness after splenectomy indicates that the spleen normally causes increased spheroidicity of the red cells. The exact mechanism of this action has not as yet been clarified.

(*c*) *Hemolytic Index.* Possibly related to the increased resistance of the red cells after splenectomy is the lowered hemolytic index, which was found in nearly two-thirds of our cases. This finding apparently persists for many years after operation, since it was present in Cases 1 and 9, splenectomized respectively 8 years and 15 years previously. As previously pointed out, the hemolytic index relates the urobilinogen excretion to the amount of pigment (total hemoglobin) from which it is derived. The total hemoglobin may be said to be a function of the individual's surface area. Normally

the hemolytic index demonstrates that 100 gm. of hemoglobin yield about 10 to 20 mg. of fecal urobilinogen per day. Heilmeyer and Oetzel[17] found that 10.3 to 22.8 mg. of urobilinogen were excreted for each 100 gm. of hemoglobin (using 16.5 gm. hemoglobin as 100%). In our investigations, figures of 11.1 to 20.8 mg. were obtained (15.5 gm. hemoglobin = 100%). That the hemolytic index is a much better indicator of the degree of blood destruction than the fecal urobilinogen output itself is brought out in Case 3, a small boy aged 10. Here, although the urobilinogen excretion was only 29.4 mg., a figure definitely lower than normal, the index of 14.6 mg. demonstrated a normal output of pigment. Only with the use of the hemolytic index is it possible to obtain a definite interpretation of the degree of destruction, particularly in small individuals and in anemia, providing, to be sure, that all the other factors of importance in urobilinogen metabolism are taken into consideration.

That the urobilinogen output in the feces may be diminished after splenectomy has occasionally been observed in previous investigations (Pearce, Krumbhaar, and Frazier,[28] Lichtenstein and Terwen,[24] Paschkis,[27] Barker,[2] Watson, *et al.*[32b] Singer,[31a] in an experimental study, found a decrease in fecal urobilinogen output amounting to about one-half the preoperative value in 50% of his splenectomized dogs. The remaining dogs failed to show any considerable change. In most of the recorded human cases, the diminished output after splenectomy was studied in patients with hemolytic anemia in which prior to splenectomy there is a greatly increased blood destruction. In our cases, normal indices after splenectomy were present in a case of Gaucher's disease and in 2 cases of congenital hemolytic jaundice (where the normal index may indeed indicate slightly increased hemolysis for a splenectomized patient). All the other cases had a low hemolytic index (with the exception of Case 15—continuing hemolysis—and the possible exception of Case 5—11.4 mg.).

Of interest was the fact that 2 of the 4 cases of congenital hemolytic jaundice showed, despite the continued presence of spherocytosis, a *low* hemolytic index. From these observations alone it would appear that spherocytes, despite their abnormal fragility to hypotonic saline, are no more readily destroyed than normal erythrocytes.

The urobilinogen excretion in the feces is the end-result of a very complicated process, and one can therefore not conclude that the urobilinogen excretion is a direct measure of hemoglobin destruction. Theoretically, the low hemolytic index found after splenectomy could be due to various causes: (1) diminished blood destruction; (2) a disturbance in the ability of the body to form bilirubin from liberated hemoglobin; (3) an increased storage of pigment. Of these possibilities, the first, namely a reduction in the breakdown of

hemoglobin, appears to be the most likely. The question arises whether the formation of target cells (which are more resistant toward hypotonic saline) may be directly correlated with the lowered hemolytic index. No direct parallelism was, however, demonstrable between the actual number of target cells and the degree of the diminution in urobilinogen output. A *general* diminution in thickness, not directly measurable, may be of greater importance in this connection than the finding of large numbers of target cells. It should be noted that target cells are present in considerable numbers in sickle cell anemia and in Cooley's anemia, conditions associated with a greatly *increased* hemoglobin destruction. Furthermore, the presence of a low hemolytic index is by no means specific for the postsplenectomized state, as this finding is present to some extent in other conditions as in iron deficiency anemia, polycythemia, hypothyroidism, and so on (*cf.* Paschkis,[27] Watson[33b]). In these conditions, however, the lowered hemolytic index can probably be interpreted as denoting an imbalance between erythrocyte formation and destruction. This will be discussed in a later paper.

5. *Studies of the lysolecithin metabolism* in our cases revealed two disturbances, *i. e.*, a frequent lack of increase of lysolecithin in the serum upon incubation and a low absolute value of lysolecithin in the peripheral blood. The latter observation has been confirmed by Gripwall.[13] It is apparent from these observations that splenectomy frequently leads to a disturbance of the whole mechanism of lysolecithin production.

*In summary*, therefore, our studies of the splenectomized individual have frequently revealed: (1) leukocytosis due primarily to an increase in lymphocytes and monocytes; (2) thrombocytosis; (3) qualitative morphologic changes in the erythrocytes—notably the presence of Howell-Jolly bodies, and target cells; (4) increased hypotonic resistance of the erythrocytes; (5) a diminution in the hemolytic index as evidenced by the relationship of the fecal urobilinogen output to the total mass of hemoglobin, and (6) disturbances in the lysolecithin metabolism.

If one takes 7 (Table 4) abnormalities which are frequently present following splenectomy (leukocytosis, thrombocytosis, Howell-Jolly bodies, target cells, increased "minimal" hypotonic resistance, lowered hemolytic index, and altered lysolecithin metabolism) and assigns to each a score of 1, a score of 7 was obtained in 1 case, and a score of 6 in 6 cases. In 3, there was a score of 5 and in 1 (a case which had been splenectomized 15 years previously), a score of only 2 was obtained. In Cases 5, 11 and 13 the data were incomplete. A normal individual has a score of 0. A score of 5 or over in a group of 7 possible factors may thus be indicative of the splenectomized state (and perhaps of a "hyposplenic" condition).

That this grouping of characteristics is *specific* for splenectomy is as yet not certain. It is possible that other conditions will be

found in which scores of "5" or over are present. Our studies have thus far, however, failed to demonstrate this. For example, in cirrhosis of the liver, in which target cells and increased resistance of the red cells are common, there is generally leukopenia, thrombocytopenia, absence of Howell-Jolly bodies, a variable hemolytic index, and a normal lysolecithin metabolism (score of 2). In Cooley's anemia and "target cell" anemia,[96] again although target cells and increased resistance are common, none of the other factors is usually present, and what is more the hemolytic index is very high. The same holds true for sickle cell anemia, in which the added factor of Howell-Jolly bodies may be present, as well as occasional leukocytosis (highest possible score 4). In polycythemia, leukocytosis, thrombocytosis and diminished hemolytic index are frequently present, but the remainder of the 7 factors are all normal. In chronic "primary" hypochromic anemia, target cells, increased resistance, and diminished hemolytic index may all be present but there is usually leukopenia and thrombocytopenia and the remaining factors are normal. In a case of probable splenic vein thrombosis, there was diminished hemolytic index and changes in the lysolecithin metabolism (score of 4), but leukopenia and thrombopenia were present. Although this scoring of abnormal factors is interesting, we recognize the danger of placing any great reliance on numerical systems of this sort. We have found it of some use to us, at least at present, in evaluating the evidence obtained in the cases studied in this investigation.

TABLE 4.—"SCORE" OF POST-SPLENECTOMY FACTORS.

| Factors. | Normal. | Case 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | 11. | 12. | 13. | 14. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Increased W.B.C. | – | + | + | + | + | + | – | + | – | – | + | + | + | – | + |
| Increased platelets | – | – | + | + | – | + | – | + | – | – | – | + | – | – | – |
| Howell-Jolly bodies | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Target cells | – | + | + | + | + | + | + | + | + | – | + | + | + | + | + |
| Increased minimal saline resistance | – | + | + | + | + | + | + | + | + | – | + | + | + | + | + |
| Diminished hemolytic index | – | + | + | – | + | – | + | + | + | + | + | + | + | + | – |
| Disturbed lysolecithin metabolism | – | + | – | + | + | Not done | + | + | + | – | + | Not done | + | Not done | + |
| SCORE | 0 | 6 | 6 | 6 | 6 | 5 of 6 | 5 | 7 | 5 | 2 | 6 | 6 of 6 | 6 | 4 of 6 | 5 |

*The Concept of "Hyposplenism" and "Hypersplenism."* In the course of our studies, we observed a case of obscure refractory anemia in which the score of abnormal factors was 4 (of the 6 factors tested). Howell-Jolly bodies and target cells were common and the hemolytic index was very low. Unfortunately, the lysolecithin

tests could not be done and a postmortem examination was not obtained. The tentative diagnosis of a possible "hyposplenic" state was made. Both Schur[30] and Schilling[29] made the diagnosis of possible atrophy of the spleen in 2 non-splenectomized cases showing large numbers of Howell-Jolly bodies. In Schilling's case, a postmortem examination was performed and showed definite atrophy of the spleen. In this connection, it should be noted that target cells are common in sickle cell anemia, in which the spleen is not infrequently atrophied.

In studies of a case showing large numbers of target cells ("target cell anemia"[96]) and many features of Cooley's erythroblastic anemia (without erythroblasts in the peripheral blood) the possibility of a "hyposplenic" condition was postulated. Target cells were also found in considerable numbers in typical cases of Cooley's anemia and in sickle cell anemia. That Cooley's anemia, "target cell" anemia, and sickle cell anemia (hemolytic syndromes unaffected by splenectomy, and with increased hypotonic *resistance*) are related diseases with the target cell as the common denominator was broached as a possibility.

That "hypersplenic" conditions may also be present is not beyond the realm of possibility. It would appear likely, as stated above, that the spleen has a "reciprocal" relationship to the bone-marrow. The increase in leukocytes and thrombocytes after splenectomy, the appearance of both Howell-Jolly bodies and target cells, all suggest this relationship. It is conceivable that splenic hyperactivity might result in a greater than normal effect upon the marrow. Were this so, leukopenia, thrombocytopenia, and increased hemolysis might result. It is interesting that in many instances of splenomegaly for whatever cause (cirrhosis of the liver, "chronic congestive splenomegaly," the Banti syndrome, infections associated with splenomegaly, notably typhoid fever, miliary tuberculosis, and so on) leukopenia and thrombocytopenia are common. To speculate further, splenic "hyperactivity" may be "total" or limited to one function ("selective"). For example, idiopathic thrombocytopenic purpura may be due to greatly increased activity of the platelet inhibiting function and hemolytic anemia to a greatly increased hemolytic function.

The possibility that splenic hormones of various types exist, some of them affecting the bone-marrow, has already been broached. The presence of Howell-Jolly bodies (improper denucleation?) after splenectomy suggests a possible relationship of the spleen to extrusion of the normoblast nucleus. Persistent leukocytosis after splenectomy suggests a relationship (inhibitory?) to leukocyte formation, and persistent thrombocytosis an inhibitory or regulatory relationship to megakaryocyte-platelet formation. These possibilities are deserving of future investigation.

**Summary.** A hematologic study was made of 19 patients in whom splenectomy had been performed from 4 weeks to 15 years previously. A rough grouping of cases into non-hemolytic and hemolytic was made. Particular attention was paid to the question of "target" cells and increased hypotonic resistance; the fecal urobilinogen output and the "hemolytic index"; and the "lysolecithin" metabolism.

Howell-Jolly bodies in erythrocytes were a constant finding after splenectomy, and target cells—abnormally thin red cells—were usually present. The presence of the latter, together with a tendency to thinness on the part of the whole red cell population adequately accounts for the increased hypotonic resistance usually seen and is confirmatory of previous work indicating that the spleen makes red cells thicker and more fragile to hypotonic salt solutions.

A lowered urobilinogen output in the feces was commonly found after splenectomy, indicating a diminution in hemoglobin destruction, perhaps related to increased thinness of red cells. The "hemolytic index" is regarded as a more important indication of hemoglobin destruction than the urobilinogen output alone. This index is determined from knowledge of the daily fecal urobilinogen output and the total circulating mass of hemoglobin (as determined from blood volume estimations).

The lysolecithin metabolism showed definite alterations after splenectomy. These observations are confirmatory of the contention of Bergenhem and Fåhraeus who believe that this normal serum lysin is produced in the spleen.

Leukocytosis and thrombocytosis were commonly present. These findings, together with the appearance of Howell-Jolly bodies (inadequate denucleation?) suggest that splenectomy may result in the removal of certain normal inhibitory mechanisms of the spleen upon the bone-marrow.

The splenectomized state is thus characterized by the presence of a group of several abnormal factors. The possibility that "hyposplenic" and "hypersplenic" conditions are occasionally present is discussed, together with evidence indicating a hormonal regulation of certain bone-marrow functions by the spleen. These observations of splenectomized individuals indicate that the spleen has direct effects on the red cells which traverse its sinusoids and indirect effects on the hematopoietic cells of the bone-marrow.

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## HEMOPHILUS INFLUENZÆ TYPE A ENDOCARDITIS.

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Ever since the description of the so-called "influenza" bacillus by Pfeiffer[19] in 1893, reports of endocarditis caused by this organism have appeared from time to time. The disease, however, is apparently not common, because less than 40 well-authenticated cases have been recorded during the half century which has since elapsed. Austin[1] and Jehle[12] furnished the first clinical reports of influenzal endocarditis, and Horder[11] in 1909 regarded it as second only to streptococcal endocarditis in prevalence. This opinion was later favored by Libman[14] and Blumer[2], both of whom thought the influenza bacillus to be responsible for most of the cases of endocarditis not caused by streptococci. More recently, Thayer[25] estimated that only about 2.5% of all cases of endocarditis are caused by the influenza bacillus, which he ranked fifth in order of importance, giving precedence to the streptococcus, staphylococcus, pneumococcus, and gonococcus. Judging from the infrequency with which the disease has been reported, however, it would seem that even Thayer's relatively low figure may be somewhat too high.

In 1918 Malloch and Rhea[16] pointed out that many alleged cases of influenzal endocarditis probably represented errors in diagnosis due to inaccurate or inadequate bacteriologic study. Such errors obviously were unavoidable at that time since little was known

concerning influenza bacilli beyond the facts that they were Gram negative, hemophilic, and apparently antigenically heterogeneous. However, the study of accessory growth factors by Davis,[5] Thjötta and Avery,[26] Kristensen,[13] Rivers,[23a,b] and Fildes,[9a] soon afterwards disclosed that important differences among organisms of the hemophilic group could be detected by their behavior on media containing the now well known "X" and "V" factors. Moreover, certain strains of influenza bacilli were shown by Pritchett and Stillman[22] and by Fildes[9b] to possess hemolytic properties. This information formed the basis for a classification of the Hemophilus group, proposed by Valentine and Rivers[28] in 1927, which is now generally accepted and is reproduced, with slight modification (Table 1). According to this classification, strains of influenza bacilli may be sharply divided into two main groups: (1) *Hemophilus influenzæ*, which require both "X" and "V" factors for growth, and (2) *Hemophilus para-influenzæ* which require only the "V" factor.

TABLE 1.—CLASSIFICATION OF THE HEMOPHILUS GROUP.

A. Requiring both X and V* factors: *Hemophilus influenzæ*
   1. Non-hemolytic
   2. Hemolytic
B. Requiring only V factor: *Hemophilus para-influenzæ*
   1. Non-hemolytic
   2. Hemolytic
C. Requiring only X factor: *Hemophilus canis*
D. Requiring neither X nor V factors: *Hemophilus pertussis*

* The "X" factor is heat-stable and associated with the iron-bearing portion of the hemoglobin molecule. The "V" factor is heat-labile and has been found by Lwoff and Lwoff[15] to be identical with Warburg's co-zymase.

For many years influenza bacilli were thought to be antigenically heterogeneous, but not long ago Pittman[20] and Platt[21] showed that freshly isolated "smooth" strains of *H. influenzæ* develop capsules which contain specific soluble substances of carbohydrate nature, in a manner similar to pneumococci. Such strains may be divided by serologic methods into 6 types, designated a, b, c, d, e and f. More recently, Chandler, Fothergill, and Dingle[3] demonstrated that *H. influenzæ* exhibits the M-S-R variation of Dawson,[6] and that capsules are produced and type-specificity is developed only in the mucoid phase. These important findings readily explain the observation, emphasized by Topley and Wilson,[27] that apparently smooth strains of *H. influenzæ* frequently are antigenically nonspecific. So far as is known, strains of *H. para-influenzæ* never develop a mucoid phase and are therefore never type-specific. A summary of the important differences between *H. influenzæ* and *H. para-influenzæ* is given in Table 2.

In the light of these facts concerning influenza bacilli it is of interest to note that all adequately studied cases of influenzal endocarditis thus far reported have been found to be caused by *H. para-influenzæ*, and according to Miles and Gray[17] there is no

case on record in which *H. influenzæ* which required both "X" and "V" growth factors has been isolated from an endocardial infection. Recently this opinion was endorsed by Craven, Poston, and Orgain,[4] who carefully reviewed the literature, and were able to collect only 36 cases, including 2 of their own, in which the clinical, pathologic, and bacteriologic data were sufficient to warrant the diagnosis of influenzal endocarditis. Craven and his colleagues state, indeed, that the 4 cases reported by Miller and Branch,[18] DeSanto and White,[8] and Fothergill *et al.*,[10] were caused by hemolytic *H. influenzæ* which required "X" and "V" factors, but they agree that there are no cases which fulfill the requirements for inclusion in the non-hemolytic group. However, an examination of the papers by Miller, DeSanto, Fothergill, and their associates, reveals no mention whatever of the use of "X" and "V" media, and moreover, in the opinion of the author, the organisms which they described were probably *H. para-influenzæ*.

TABLE 2.—COMPARISON OF HEMOPHILUS INFLUENZÆ WITH HEMOPHILUS PARA-INFLUENZÆ.

| | *H. influenzæ*. | *H. para-influenzæ*. |
|---|---|---|
| Morphology | Cocco-bacilli with occasional rods and filamentous forms | Marked pleomorphism; rods and filaments predominate |
| Accessory growth factors | Requires both "X" and "V" factors | Requires only "V" factor |
| Action on blood agar | Usually non-hemolytic | Not infrequently hemolytic |
| Action on carbohydrates | Fermentative powers usually slight | Usually wider range of fermentative powers |
| Action on tryptophan | Most strains produce indole | Most strains fail to produce indole |
| Pathogenicity for animals | Mucoid strains pathogenic for mice and rabbits | Comparatively less pathogenic for mice and rabbits |
| Antigenic classification | Mucoid strains elaborate capsules containing specific soluble substances and may be classified antigenically as Types a, b, c, d, e, and f | Antigenically heterogeneous; no capsule formation |

Since no authentic case of bacterial endocarditis caused by typical *H. influenzæ* has been previously recorded, it has been impossible, as pointed out by Miles and Gray,[17] to compare the known para-influenzal endocarditis with the influenzal variety. The following example of true influenzal endocarditis is therefore reported.*

**Case Report.** H. R., No. 588159, a 19-year-old, single, electrical worker, was admitted to the Presbyterian Hospital on August 25, 1939. The patient's chief complaints were weakness, fatigue, and night sweats of 3 months' duration. He had also had fever for 1 week prior to admission.

One brother developed rheumatic heart disease when 5 years old and died at the age of 22, apparently of subacute bacterial endocarditis. The remainder of the family history was non-contributory.

The patient had in general enjoyed good health until the onset of the present illness. He had never suffered from any acute infectious diseases

* The author is indebted to Dr. Robert F. Loeb and Dr. James W. Jobling for permission to report this case.

of note. At the age of 9 he was seen in the Vanderbilt Clinic with complaint of swelling and stiffness of the right knee. He was found to be afebrile but no other details of this incident remain available. Two years later, when aged 11, he was treated in the clinic for an acute left maxillary sinusitis which rapidly subsided. Examination of the heart and lungs at that time revealed nothing definitely abnormal. Throughout the succeeding 8 years he apparently enjoyed excellent health and was able constantly to participate in various forms of strenuous athletics.

Three months before entry the patient suddenly developed excruciating pain in the left cheek. Examination showed some tenderness over the left maxillary region, and the Roentgen ray revealed slight clouding of the left antrum. The antrum was punctured for drainage, but the washings appeared clear and unfortunately no culture was taken. The pain subsided within a few days without further treatment. Shortly following this episode the patient noted gradually increasing weakness, lethargy, and fatigue, accompanied by frequent drenching night sweats. Three weeks before admission his right ankle became painful, hot, and swollen. He was seen at another hospital where a diagnosis of rheumatic fever was made. The swelling and pain in the right ankle gradually disappeared over a period of 2 weeks. Nine days before entry the patient was seen in the dispensary, where examination of the heart and lungs disclosed no abnormal findings. Weakness, fatigue, and night sweats continued, and for the week previous to hospitalization he had a constant fever ranging as high as 103° F.

*Physical Examination.* On admission the temperature was 101.2° F., pulse 90, respirations 20, and blood pressure 140/40. Examination revealed a well-developed and nourished white male who did not appear acutely ill. There was no dyspnea, orthopnea, cyanosis, edema, or jaundice. A visible pulsation was noted in the suprasternal notch. The mucous membranes appeared somewhat pale. No petechiæ could be discovered. The finger-tips were neither clubbed nor tender.

The heart was enlarged to the left by percussion and a forceful, heaving apex impulse was palpated 12 cm. to the left of the midsternal line in the 5th interspace. On auscultation over the apical area there was a faint, short, pre-systolic murmur with a snapping first sound, followed by a loud, blowing systolic murmur transmitted to the left axilla. A rumbling diastolic murmur in early and mid-diastole was also detected. Over the aortic area could be heard a rather harsh systolic murmur, transmitted well to the neck vessels, followed by a blowing diastolic murmur which almost completely obliterated the second sound. The lungs were clear. The pulse was of the Corrigan type.

The abdomen was relaxed and soft. The liver could not be palpated and was not enlarged to percussion. The spleen was slightly enlarged, firm, smooth, and non-tender. The remainder of the physical examination was not remarkable.

*Laboratory Findings.* Examination of the blood revealed a hemoglobin of 9.5 gm. (Sahli), an erythrocyte count of 3,900,000, and a leukocyte count of 9600. The differential count showed neutrophils 77%, lymphocytes 17%, monocytes 5%, and eosinophils 1%. The erythrocyte sedimentation rate was 80 mm. in 1 hour, using the Westergren method. The Kline test was negative. The urine showed no albumin, sugar, or casts, and contained only a few leukocytes. A Roentgen ray film of the chest taken at a distance of 2 meters showed an enlarged cardiac silhouette with the following measurements: MR 3.5 cm., ML 10.8 cm., TD 14.3 cm., GV 5.8 cm The internal diameter of the chest was 27.5 cm. The configuration of the heart shadow suggested that seen with aortic valvular lesions. The electrocardiogram exhibited form changes indicative of definite heart muscle damage. The P–R interval was 0.15 seconds, with normal sinus rhythm. A blood

culture taken on the day of admission showed no growth after incubation for 2 weeks.

The admission diagnosis was: Rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and insufficiency, subacute bacterial endocarditis.

*Course.* During the patient's first admission he had surprisingly few symptoms and in general his condition remained good. He did, however, have a constantly elevated rectal temperature ranging from 99.6° to 101.8° F. The leukocyte count, repeated at frequent intervals, was moderately elevated from 11,480 to 16,150, with 67 to 77% neutrophils. The diastolic pressure remained constantly low, and the blood pressure readings varied between 120/25 to 140/40. From time to time he complained of feeling weak and tired, and occasionally he had a profuse diaphoresis associated with upward swings in temperature.

Four days after entry (Aug. 29) localized areas of tenderness developed suddenly over the left elbow and at the tip of the left index finger, with slight redness and swelling. Two days later the spleen was found to be somewhat larger, but still non-tender. Petechiæ appeared for the first time in the lower conjunctivæ on Sept. 10. Meanwhile the auscultatory findings in the heart had changed, and the snapping apical first sound could no longer be heard, while the heart tones at the apex had become almost entirely replaced by a continuous murmur.

In spite of the apparently clear-cut evidence of bacterial endocarditis, 6 blood cultures taken between the date of admission and Sept. 11 all failed to show growth, although none was discarded before 2 weeks of incubation.

Chemotherapy with sulfanilamide was begun Aug. 30 and continued until the patient's discharge, 52.8 gm. being administered over a period of 12 days. Blood concentrations of the free drug ranged from 3.0 to 6.4 mg. per 100 cc. The sulfanilamide was well tolerated, but it failed completely to effect any improvement in the condition of the patient.

Arrangements in the meantime had been made for terminal care and the patient was discharged to his home on Sept. 11, the 18th hospital day, with admission diagnosis unchanged.

*Interval Note.* The patient was seen in the Vanderbilt Clinic on Sept. 21, at which time he had gained 9 pounds and stated that he felt much better. However, on the preceding evening he had experienced a sudden, sharp pain in the right heel followed by a temperature rise to 102° F. He was seen again a week later, and still felt fairly well, but temperature had remained elevated, with daily rises to 101° to 102° F. On physical examination no new findings were observed. The hemoglobin was 13.1 gm., erythrocyte count 4,850,000, and leukocyte count 11,800 (neutrophils 70%, lymphocytes 24%, and eosinophils 6%). The erythrocyte sedimentation rate had dropped to 35 mm. in 1 hour. A blood culture again failed to show growth.

On Oct. 14, 5 weeks after discharge, he suddenly developed severe pain in the left upper quadrant, unaccompanied by nausea or vomiting. The pain continued without relief, and shortly thereafter he returned to the hospital.

*Final Admission.* The patient was readmitted on Oct. 17, 1939. On entry the temperature was 102° F., pulse 120, respirations 26, and blood pressure 130/0.

*Physical Examination.* The patient now appeared acutely ill with marked pallor and cyanosis of the skin and mucous membranes. There was moderate dyspnea and orthopnea. Petechiæ were noted in the lower conjunctiva of the right eye. Capillary pulsation could be readily seen in the nail beds. The heart was enlarged 12 cm. to the left in the 5th interspace

with a heaving apical in pulse. On auscultation at the apex a short presystolic murmur was heard, followed by a loud, harsh systolic murmur well transmitted into the left axilla. Over the base a harsh systolic murmur was heard, followed by a short, high-pitched diastolic whiff. No pericardial friction rub could be detected. The lungs were clear except for a few frank medium râles at the left base posteriorly. The abdomen was moderately distended. A smooth, slightly tender liver was palpated 4 finger-breadths below the right costal margin. A tender, moderately enlarged spleen could also be felt. No other significant observations were made on physical examination.

*Laboratory Findings.* The blood showed a hemoglobin of 11.0 gm., erythrocyte count 4,570,000, and leukocyte count 23,840 (neutrophils 86%, lymphocytes 11%, monocytes 2%, and eosinophils 1%). The erythrocyte sedimentation rate was 45 mm. in 1 hour. The urine contained 1+ albumin and numerous granular casts, but no leukocytes or red cells. A blood culture yielded growth of *H. influenzæ* in both flasks after incubation for 4 days.

*Course.* On admission the patient was restless and apprehensive with almost complete disorientation. Dyspnea and cyanosis were marked, with the respiratory rate varying from 25 to 40 per minute, and oxygen therapy only slightly alleviated the respiratory distress. The rectal temperature remained elevated, ranging from 101.2° to 102° F.

On Oct. 18, the day following admission the patient was worse and the white count had risen to 38,900, with 89% neutrophils. Venous engorgement appeared marked and the dyspnea and cyanosis were unrelieved. However, the lungs were surprisingly clear.

On Oct. 19 the patient was rational and more comfortable. A portable Roentgen ray of the chest revealed cardiac enlargement and evidence of fluid at both bases. The findings in the electrocardiogram were strikingly different from those previously observed. Deformity of the *QRS* complexes was present in all leads with a prominent $Q_1F$. $T_1$, $T_2$, and $T_1F$ were upright, while $T_3$ was inverted. The P–R interval was 0.16 seconds. The changes indicated a marked disturbance of ventricular conduction. The venous pressure was 310 mm. of water.

On Oct. 20 the patient was worse again and appeared very restless, as well as more dyspneic and cyanotic. The white blood count had further increased to 40,280, with 85% neutrophils. Examination revealed that while the upper trunk and extremities were cold, livid, and cyanotic, the legs and feet were warm and pink. The cyanosis of the lips, face, chest, and abdomen was striking. There was puffiness of the face and upper back with distention of the neck veins. The lungs were remarkably clear. The cardiac findings were unaltered. The liver was tender and enlarged to the level of the umbilicus. Following a brief period of augmented restlessness the patient suddenly expired.

*Final Diagnosis.* Rheumatic heart disease, mitral and aortic stenosis and insufficiency, subacute bacterial endocarditis, cardiac decompensation, chronic passive congestion of liver and spleen, infarction of spleen, and thrombosis of superior vena cava.

*Autopsy.* (Autopsy No. 13193, 2½ hours postmortem by Dr. W. H. Carnes). Examination was restricted to an 8-inch abdominal incision through which the contents of the thoracic cavity were removed en bloc, together with the aorta, trachea, and larynx. The pleural surfaces were smooth and there were no pleural adhesions. The pericardial cavity contained no excess of fluid and its surfaces appeared normal. The superior vena cava was removed in its entirety and contained no thrombus. The jugular veins were empty.

*Heart.* The heart was very large and weighed 510 gm. The epicardium itself was not remarkable, but near the apex of the heart, overlying the

anterior portion of the interventricular septum, there was a small, lenticular elevation about 5 mm. in diameter. Section through this showed an oval, encapsulated, reddish-gray mass of thrombus which appeared to lie in a tiny aneurysm of one of the coronary arteries.

On opening the heart both the right and left ventricles were found to be greatly dilated and hypertrophied. The right auricle appeared normal, but the left auricle was considerably dilated and showed hypertrophy of its wall. There were no thrombi in the auricular appendages. The tricuspid and pulmonary valves were normal. The aortic valve was anomalous and possessed but 2 cusps, the coronary arteries being centrally placed in the sinuses of Valsalva. The left cusp had been largely destroyed by a bacterial infection and was the seat of large, yellow, fungating vegetations which had completely replaced its posterior half. The vegetations had also spread upward into the neighboring sinus of Valsalva, and downward onto the

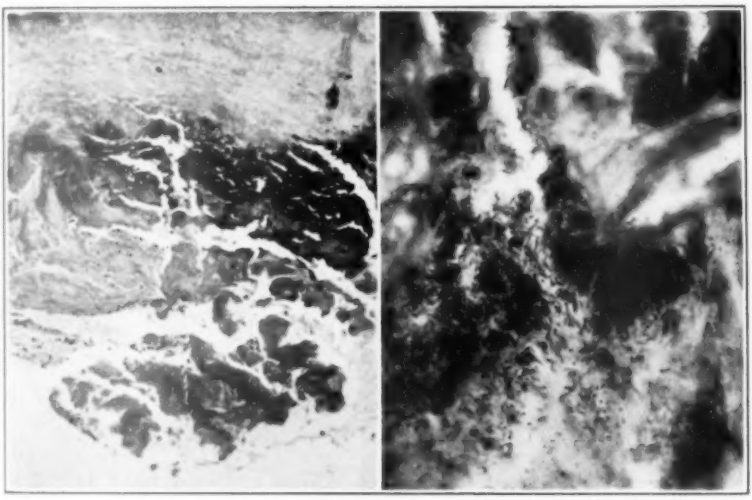

FIG. 1 FIG. 2

FIG. 1.—Bacterial vegetation of aortic valve.
FIG. 2.—*Hemophilus influenzæ* in vegetation of aortic valve.

aortic leaflet of the mitral valve, which showed several small, unperforated mycotic aneurysms. The mitral valve was otherwise normal and there was no evidence whatever of antecedent rheumatic involvement.

*Microscopic* examination of a section made through the base of the aortic vegetation showed it to be composed of eosinophilic necrotic material almost devoid of cells, with patches of dense calcium deposition about its lower border (Fig. 1). Intermingled with these patches of calcification and covering virtually the entire surface of the vegetation were large colonies of bacteria. Sections stained with methylene blue, under higher magnification, showed masses of bacteria which exhibited mainly filamentous forms, although many cocco-bacilli were also present (Fig. 2).

*Gross* examination of the ventricular myocardium revealed numerous small, pale, yellowish fat deposits, but in only one place in the middle portion of the left ventricular wall was there a pinkish, translucent area suggestive of a fresh scar. The apical portion of the left ventricle was very thin, no

doubt partly due to the dilatation, but possibly also the result of nutritional disturbances consequent to the small mycotic aneurysm of the coronary artery described near the tip of this ventricle. All of the coronary arteries were carefully opened in search for emboli, but no others were found which could be recognized with the naked eye.

*Microscopic* examination of sections removed from both ventricles, revealed numerous areas of fresh necrosis of the muscle, with loss of nuclei and increased eosinophilic staining of the cytoplasm (Fig. 3). Other areas of recent destruction still contained a few infiltrating inflammatory cells. One focus of older destruction showed mainly acellular connective tissue with numerous small blood-vessels (Fig. 4). In spite of the extensive myocardial damage bacterial emboli were found in only 2 small coronary arterioles. In addition a section through the small mycotic aneurysm at the apex of the left ventricle showed clearly the origin from the tiny coronary

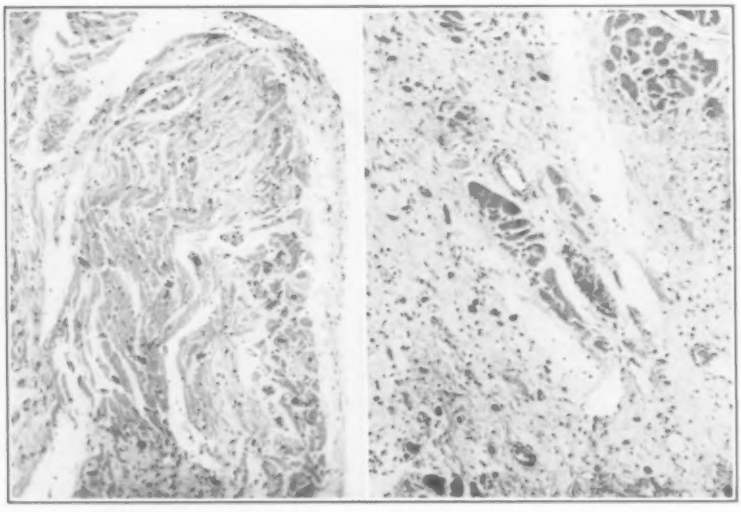

FIG. 3 FIG. 4

FIG. 3.—Focal necrosis of myocardium.
FIG. 4.—Healed focus of myocardial degeneration.

branch accompanying it. At the point of emergence of the vessel from the aneurysm its wall was greatly thickened eccentrically by a mass of calcified material. The aneurysm itself was entirely filled by old, autolyzing thrombus material in which no bacteria could be recognized (Fig. 5).

Sections through the interventricular septum showed changes similar to those observed in the ventricular myocardium, but less severe. The left auricle appeared normal.

*Lungs.* The right and left lungs weighed 540 gm. and 480 gm. respectively. On section the pulmonary tissue did not ooze fluid to any considerable extent, but there was a mottled, rusty appearance to the cut surface characteristic of chronic passive congestion. No areas of consolidation were seen and none of the vessels contained thrombi.

*Microscopic* examination showed all the alveoli to be filled with great numbers of large mononuclear phagocytes, which, however, contained little if any visible pigment. There was no edema.

*Spleen.* The organ was large and swollen, and weighed 380 gm. Beneath the capsule were irregular, raised areas varying from one to several centimeters in diameter, which on section proved to be rather fresh infarcts. The Malpighian bodies were unusually conspicuous. The splenic artery and vein appeared normal.

The microscope revealed marked chronic passive congestion, as evidenced by thick pulp cords and prominent distended sinusoids. The larger infarcts showed necrosis and considerable autolysis in their deeper portions; with scattered accumulations of neutrophils at their margins. Two fairly large branches of the splenic artery were plugged by organizing thrombi.

*Liver.* The liver weighed 2100 gm. and on section presented the classical "nutmeg" appearance of chronic passive congestion. Microscopic examina-

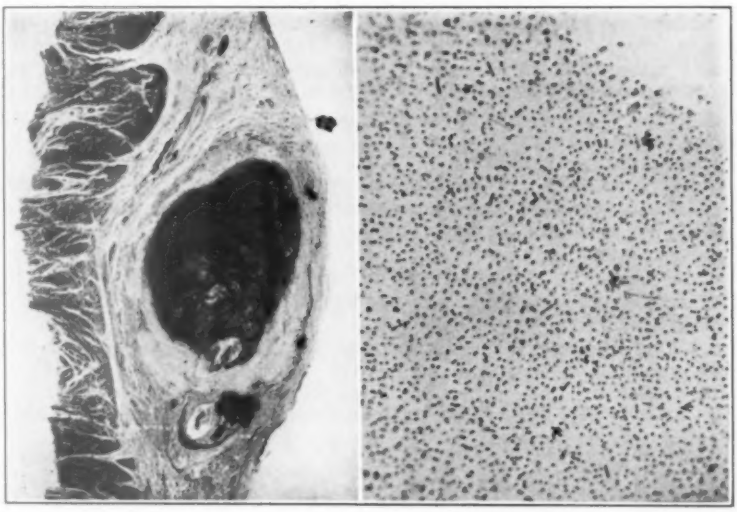

FIG. 5 FIG. 6

FIG. 5.—Mycotic aneurysm of coronary artery.
FIG. 6.—Gram-stained preparation of 18-hour culture of *H. influenzæ* in Levinthal's broth.

tion showed large areas of atrophy or necrosis occupying the central portion of the lobules. There were hemorrhages into the collapsed framework where liver cells had disappeared.

*Kidneys.* The right and left kidneys weighed 185 gm. and 220 gm., respectively. The surfaces of each displayed large, pitted scars of healed infarcts measuring 1 to 3 cm. in their greatest dimensions. On section additional small, reddish areas of fresh infarction were seen. No hemorrhages were observed. The pelves, calices, and ureters were not unusual.

Microscopic section showed old and recent emboli in the interlobular arteries supplying the areas of infarction. Embolic lesions of the glomeruli were absent.

The remainder of the gross and microscopic examination failed to disclose anything of significance.

*Bacteriologic Findings.** The organism was isolated from both flasks of a blood culture taken on Oct. 17, 1939, 3 days before the death of the patient, and also from the heart's blood and a well-washed portion of aortic vegetation obtained postmortem.

For the antemortem blood culture two 5-cc. portions of the patient's venous blood were each seeded into 100 cc. of a beef heart infusion broth containing 1% neopeptone and 0.5% dextrose. In these cultures growth first appeared on the 4th day as a diffuse clouding of the media. Microscopic examination of Gram-stained preparations revealed numerous small Gram-negative bacilli and cocco-bacilli, with an occasional longer rod or filamentous form. Identical findings were obtained from a culture of heart's blood taken during the necropsy, as well as from a portion of the aortic vegetation which was repeatedly washed in saline and incubated in nutrient broth containing defibrinated rabbit's blood.

The results of further study of this strain may be summarized as follows:

*Morphology.* Repeated subculture on Levinthal's agar showed the morphology to be remarkably stable. Gram-stained smears of colonies chosen after 12 to 18 hours incubation invariably showed mainly small Gram-negative bacilli or cocco-bacilli with few rod or filamentous forms (Fig. 6).

*Plain Agar.* No growth.

*Plain Broth.* No growth.

*Sheep Blood Agar.* No growth. However, when plates were inoculated simultaneously with *Staph. aureus*, good growth occurred with typical satellite phenomena. No hemolysis.

*Rabbit Blood Agar.* Good growth in 18 hours. Colonies 0.5 to 1.5 mm. in diameter, tended to be confluent, and appeared flat, watery, and smooth, with slightly serrate edges. The cultures smelled strongly of indole. No hemolysis.

*Levinthal's Agar.* In 18 hours colonies were 1 to 3 mm. in diameter, flat, glistening, and somewhat opaque. By transmitted light the colonies showed marked iridescence. Odor of indole pronounced.

*X and V Media.* The results may be summarized in the following table:

| *Media.* | *Growth.* |
|---|---|
| Nutrient agar + autoclaved Levinthal broth (X factor) | 0 |
| Nutrient agar + yeast extract (V factor) | 0 |
| Nutrient agar + autoclaved Levinthal broth + yeast extract (X + V factors) | + + + + |

*Fermentation Reactions.* Fermentation tubes to which Levinthal's broth had been added were employed. The organism produced a small amount of acid from dextrose but did not attack mannite, lactose, saccharose, salicin, maltose, or xylose.

*Indole Production.* Large amounts of indole were formed in peptone water to which Levinthal's broth had been added.

*Antigenic Classification.* Organisms removed from cultures on Levinthal's agar at the end of 6 hours showed a clear-cut Quellung reaction with Type a *H. influenzæ* rabbit antiserum. No capsule swelling was observed with Type b antiserum.

Precipitin reactions were also carried out with 6-hour cultures. Heavy suspensions of the organisms were made in normal saline, shaken thoroughly, and centrifuged. The clear supernatant fluid was then layered over Type a and Type b antisera. With the Type a serum a good immediate ring was observed, with heavy precipitate at the end of 24 hours. The reaction with Type b anti-serum was negative.

* The author wishes to thank Dr. Hattie Alexander and Miss Katherine C. Mills for their assistance in identifying the organism.

*Pathogenicity.* Unfortunately no adequate study was made of pathogenicity. One Swiss mouse inoculated intraperitoneally with 0.5 cc. of an 18-hour Levinthal broth culture succumbed within 24 hours. No other animals were inoculated.

**Comment.** The clinical course and pathologic findings in this case of *H. influenzæ* endocarditis did not differ significantly from those observed by others in subacute bacterial endocarditis caused either by *H. para-influenzæ*[4,17] or *Strep. viridans*.[2,25] The infection apparently originated in the maxillary sinus, with subsequent implantation on a congenitally anomalous aortic valve. This was followed by a prolonged febrile course, repeated embolic phenomena culminating in splenic infarction, and terminal acute myocardial insufficiency. In the final hours of the illness a rather striking polymorphonuclear leukocytosis developed, accompanied by physical findings suggestive of thrombosis of the superior vena cava. At necropsy, however, no thrombosis of this vessel could be demonstrated, and the lack of pulmonary edema, coupled with the evidence of marked passive congestion of the liver and spleen, indicate that these findings were due primarily to extreme right heart failure. The high leukocytosis must be explained chiefly on the basis of the extensive splenic infarction and necrosis, since elsewhere acute inflammatory changes were remarkably scant. The myocardium, while showing numerous areas of recent degeneration and scarring, showed fewer evidences of embolization of the coronary arteries than have been reported in *Strep. viridans* endocarditis.[7,24] The one small mycotic aneurysm of a coronary arteriole was not of recent origin. The localization of the bacterial infection on the bicuspid aortic valve is worthy of special note, since it adds emphasis to the well-established fact,[2,17,25] that antecedent injuries (*e. g.*, rheumatic) or congenital abnormalities of the heart valves are almost a *sine qua non* in subacute bacterial endocarditis, regardless of the nature of the infecting agent.

The total duration of the illness, which lasted approximately 5 months, is of some interest in the light of the suggestion by Craven, *et al.*,[4] that endocarditis due to *H. influenzæ* may be more acute than that due to *H. para-influenzæ*, and that the non-hemolytic varieties of the 2 species produce more rapidly progressive endocardial infections than do their hemolytic relatives. It would seem from this case, in which the course was typically subacute, that until further evidence has been gathered the classification of influenzal endocarditis must remain strictly a bacteriologic one, since thus far no striking differences have been observed between true influenzal infection on the one hand, and para-influenzal infection on the other.

**Summary.** 1. A fatal case of subacute bacterial endocarditis caused by *Hemophilus influenzæ*, Type a, with implantation on a

bicuspid aortic valve, is reported. This is apparently the first case record of proved endocardial infection with this organism.

2. The clinical course and pathologic findings in this case do not differ significantly from those previously described in *H. parainfluenzæ* endocarditis.

3. A brief period of chemotherapy with sulfanilamide failed to affect the outcome of the disease.

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## CRITICAL RATES IN VENTRICULAR CONDUCTION.

### UNSTABLE BUNDLE BRANCH BLOCK.

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CONDUCTION in the ventricles of a normal heart as expressed by the *QRS* complex of the electrocardiogram is a stable phenomenon. During the 40- to 50-year span of adult life this function is remarkably constant in the absence of heart disease, the *QRS* varying little if at all. Even considerable increases in rate of the normal heart fail to alter significantly the contour of this complex.

Several factors are believed to be concerned with this stability of function. One is the relatively smaller blood supply to the conduction tissue, which is said to be one-half that to heart muscle fiber.[22] A second is the resistance of this tissue to anoxemia,[6,16,24] and a third

factor is vagal control.[7,15,20,23] All these and other factors, such as nervous chemical, and mechanical influences,[5] need clarification.

Impairment of the circulation to the bundle of His and its branches is a fairly common occurrence in the course of disease of the coronary arteries. Often an expression of this condition is block in a branch of the bundle. Some idea of its frequency can be obtained from the observation by King[9] that at the Johns Hopkins Hospital bundle branch block was seen more often than rheumatic fever. In a period of 5 years it was one-quarter as common as auricular fibrillation, three times as common as auricular-ventricular block, and four times as common as auricular flutter.

The usual type of bundle branch block is permanent, even though this be over a period of many years.

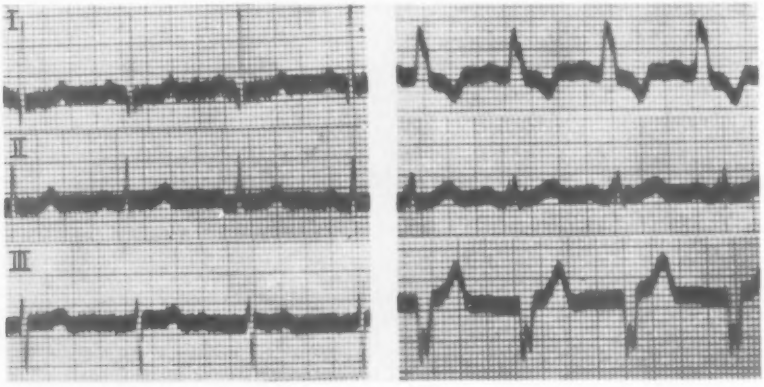
Bundle branch block may be transient. This type was first described by Lewis[12a] in 1913. It has been reported many times since and is not rare. As in the case reported by Lewis, what usually occurs is that a patient who has developed bundle branch block, improves and eventually normal ventricular conduction is restored. Here there has been only one continuous episode of block.

Another form of transient bundle branch block has been described (Hermann and Ashman[5]), wherein many fluctuations back and forth between normal conduction and block take place. Responsible for these vacillations are several causes including changes in rate. The following report is concerned with this type of transient bundle branch block with frequent fluctuations between good conduction and block due to variations in rate. The changes are almost always complete within the duration of a single cycle, one *QRS* being normal and the next being that of bundle branch block, or the reverse. At a certain cardiac rate the equilibrium between normal ventricular conduction and block is so delicate that it is frequently disturbed and several changes back and forth may take place within the period of a minute or two. These changes are caused by such slight alterations as an increase or decrease in the heart rate of only one or two beats per minute. There is then a critical rate at which the appearance or disappearance of bundle branch block can be brought about by these very slight alterations in rate. Two such cases are described below, one in which the increase in rate of one beat or more per minute induced bundle branch block from normal ventricular conduction; the other in which a decrease in heart rate of one beat or more per minute acted similarly when the ventricle was beating at a certain rate.

**Case Abstracts.** CASE 1.—P.Y., admitted to the hospital (service of the late Dr. M. A. Rothschild) Dec. 12, 1930, was Russian, 49 years old and had 4 children. There was no history of any disease in childhood; she did not recall having had rheumatic fever or chorea. Venereal disease was denied. Symptoms of the menopause started in 1926. The present illness had its onset at about that time. She complained of spells of dizziness, buzzing

in the head, spots before her eyes, and a consciousness of her heart beat associated with some precordial pain. She was told her blood pressure was 170. After a short hospitalization she returned home and was able to perform most of her household duties. She did so for the next 4 years until 6 weeks before her admission to this hospital when she had an attack of pain over the precordium and with this a return of all the previous symptoms. The pain was moderately severe and radiated from the lower end of the sternum up to the throat. It lasted about 1 hour. Similar attacks of shorter duration occurred about 5 to 6 times daily and were usually brought on by effort. In this 6-week period she noticed very frequently during the day a peculiar, sudden, and momentary tinkling sensation inside her chest in the region of the left breast.

On examination, the patient did not appear ill and was quite comfortable lying in bed. Her temperature was 99.6° F., pulse rate 102, and respirations were 24 per minute. There was no dyspnea, orthopnea or cyanosis. The retinal vessels were thinned. The heart was not enlarged on Roentgen examination. When the patient was in the recumbent position the heart




*a* *b*

FIG. 1.—Case 1. Leads I, II, and III. (*a*) The patient in recumbent position; heart rate, 67 to 71 per minute; *QRS*, normal. (*b*) The patient standing; heart rate, 79 to 87 per minute; bundle branch block.

sounds were normal. The blood pressure was 180/100. The lungs were clear. The liver edge was palpable 3 fingers below the costal margin. There was slight bilateral pretibial pitting edema. The routine examination of the urine, complete blood count, and blood non-protein nitrogen were within normal. The electrocardiogram taken in the recumbent position was within normal except possibly for the *Q* wave in Lead 1 (Fig. 1*a*).

*Clinical Diagnosis.* Hypertensive and arteriosclerotic heart disease, coronary sclerosis, coronary occlusion(?), myocardial fibrosis, angina pectoris.

The patient remained in the hospital 2½ weeks. After the first few days she became very uncoöperative. She left the hospital against advice, her condition little changed.

*Observations.* With the patient sitting up in bed and connected to Lead 1 of the electrocardiograph, the string shadow was seen to perform short runs of two different types of excursions which alternated frequently, paroxysms of each lasting from several beats to several minutes. From a knowledge of previously taken records, it was readily apparent that the complexes, consisting of quicker and shorter *QRS* excursions and an upright *T* wave,

were those of normal conduction, and that the slower excursions of longer duration with the *T* wave directed downward were those of bundle branch block.

While the patient remained in the recumbent position the ventricular conduction was normal, the *QRS* being of the normal variety (Fig. 1*a*). While the patient was standing, the *QRS* waves were all of the bundle branch block type (Fig. 1*b*). When the patient was sitting, frequent fluctuations between the two types of *QRS* were observed with paroxysms of each of varying length.

Other maneuvers were carried out and their effect on the *QRS* observed. These were: inspiration and expiration with the patient recumbent, sitting, and also standing, exercise, carotid sinus pressure, and injections of atropine and pilocarpin.

Many changes back and forth between normal ventricular conduction and bundle branch block were recorded. When the rate was measured, it was seen that there was a close relationship between the ventricular conduction and cardiac rate. At slower rates ventricular conduction was normal; at faster rates bundle branch block was present. This was so, regardless of postural changes, respiratory variations and other maneuvers except insofar as they affected the rate of the heart.

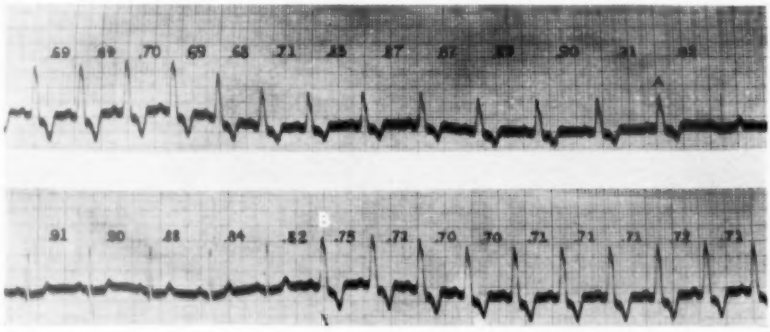



FIG. 2.—Case 1. Lead I. Arabic numbers are the *R–R* intervals in seconds. The patient in recumbent position after exercise. As the cardiac rate slows bundle branch block reverts to normal, after complex A, when the *R–R* interval increases from .91 to .92 second. At *B* there is a return to bundle branch block as the cardiac rate increases and the *R–R* interval is reduced from .84 to .82 second.

With the patient in the recumbent position following exercise, the ECG was recorded as the cardiac rate gradually slowed (Fig. 2). *R-R* intervals gradually increased from 0.68 to 0.91 sec. up to complex A. During 37 such cycles each *QRS* was of the bundle branch block type. As the slowing continued the next *R–R* interval was 0.92 sec., an increase of 1/100 sec. The *QRS* suddenly became normal and remained so during 7 beats while the *R–R* intervals ranged between 0.92 and 0.84 sec. The rate again grew faster. As the *R–R* interval decreased from 0.84 to 0.82 sec. there was a sudden change to bundle branch block (*B*) which persisted during the next 16 complexes with the *R–R* intervals between 0.82 and 0.68 sec. Thus before the first change, (*A*) bundle branch block was present at all rates faster than 65 beats per minute and after the second change (*B*) at all rates faster than 71 per minute. The change from block to normal conduction was sudden and complete within the period of one cycle. Though the transition was not gradual, there were some variations in the *QRS* and *T* complexes, readily seen 8 cycles before the change to normal conduction.

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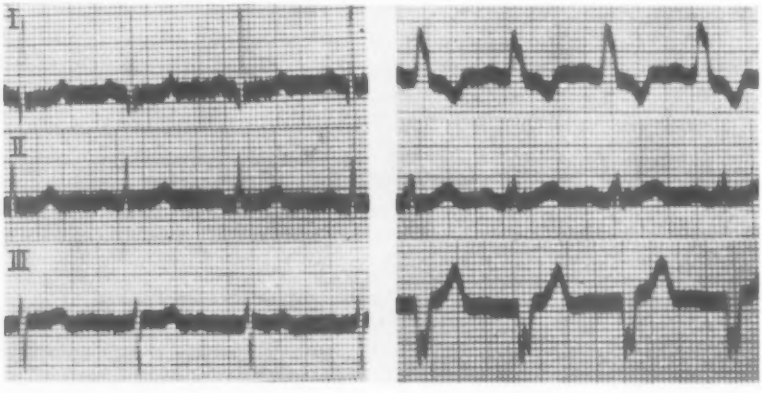


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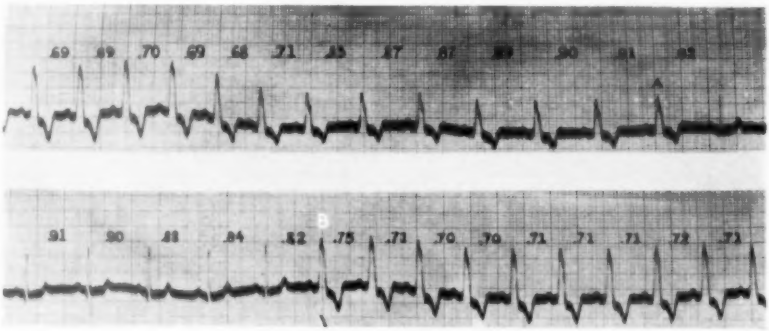


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At other times the critical cardiac rate was observed to be 72, 73, 75 and 76 beats per minute, with bundle branch block when these rates were exceeded.

Four changes between conduction and block with variations of rate are illustrated in Figure 3.

The heart sounds at the apex were listened to by one observer* while another was watching the string shadow on the camera face. During normal ventricular conduction the first sound at the apex was clear, of medium pitch, moderately loud and not accompanied by a murmur. When bundle branch block was present the first sound was impure, much lower in pitch and intensity, and was immediately followed by a low-pitched, rumbling, systolic murmur lasting through one-half of systole. These sounds were observed many times. Each was always found true to one type of ventricular conduction and was regularly associated with it.

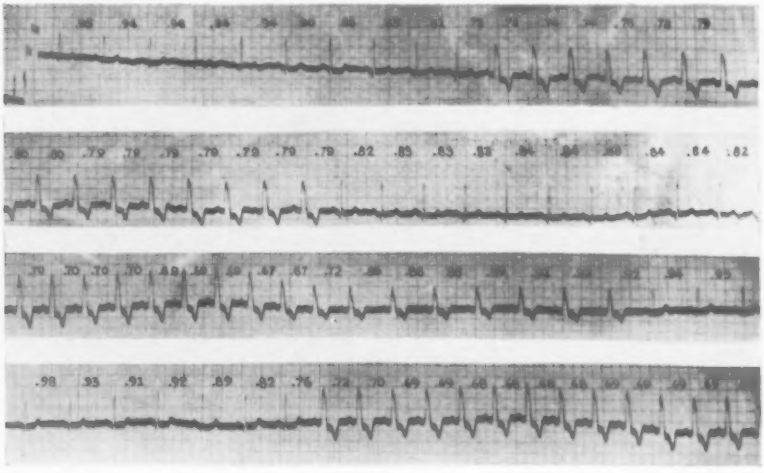

FIG. 3.—Case 1. Lead I. Four changes in conduction occurring during variations in cardiac rate are illustrated.

Frequently at the instant of change in conduction as noted by the change in heart sounds or motion of the string shadow of the electrocardiogram, the patient said she felt a sudden "tinkling" sensation in her chest.

The blood pressure was taken while the patient was in the sitting position when changes in the type of ventricular conduction were occurring. The blood pressure remained the same during normal conduction, during block, and during the transitions.

CASE 2.—E.B., admitted to the Beth Israel Hospital (service of Dr. I. W. Held) on April 15, 1940, was 50 years old, married, and had 2 children. Eight years ago she received treatment in the hospital for mild hyperthyroidism. The basal metabolic rate was +32.

The present admission to the hospital was due to an attack of an upper respiratory infection with fever, sore throat, cough, and pains in the arms and legs. On examination the temperature was 103.2° F.; pulse 64, and the respiratory rate 28. She appeared to be acutely ill. The pharynx was reddened. Neck veins were full. The lungs were clear. The heart was

* With the assistance of Dr. David Ball.

enlarged to the left. The cardiac rate was completely irregular but without a pulse deficit. A loud harsh systolic murmur heard at the apex was transmitted well to the axilla. $P_2$ was louder than $A_2$ and was accentuated. The blood pressure registered 124/58. Venous pressure was 18 cm. of water by direct measurement in an antecubital vein. The liver could not be definitely palpated. There was no edema, cyanosis or clubbing. Retinal arteries were narrowed.

*Clinical Diagnosis.* Acute upper respiratory infection. Arteriosclerotic heart disease, coronary sclerosis, myocardial fibrosis, auricular fibrillation, Class IV (new classification*). There was a moderate leukocytosis; 18,000, 69% neutrophils; a slight anemia, 4 million red blood cells and 70% hemoglobin. Erythrocyte sedimentation rate was 25 mm. in 45 minutes. The

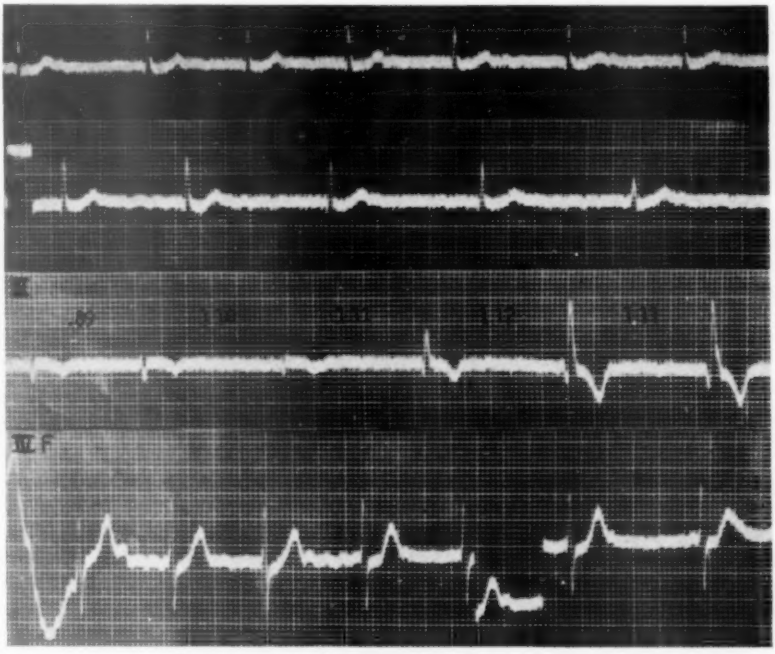

FIG. 4.—Case 2. Leads I, II, III, and IV F. The change to bundle branch block is seen in Lead III.

urine had a specific gravity of 1.020, and a slight amount of albumin. Non-protein nitrogen in the blood was 40 mg. per 100 cc. The blood culture was sterile.

The Roentgenogram revealed some general enlargement of the heart with local accentuation of the left auricular, left ventricular and right contours, also some calcification of the aortic arch and marked pulmonary hypervascularization.

The Roentgen-kymogram (Dr. I. S. Hirsch) indicated diminished amplitude of the aortic pulse wave, thought to be due to arteriosclerosis.

A four-lead electrocardiogram was taken on the day after admission (Fig. 4). There was auricular fibrillation. *RT* in Leads I, II, and IV F

* Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 4th ed., New York Heart Assn., 1939.

were depressed. In Lead III the cardiac rate slowed and there occurred one transition to bundle branch block. Here there was at least one intermediary complex of lesser block indicating a more gradual transition to apparently complete block.

An electrocardiogram taken the next day (Fig. 5) revealed 22 changes back and forth between *QRS* waves of normal duration and those of some bundle branch block in 83 complexes recorded. There were 36 normal and 47 of incomplete bundle branch block.* The longest *R–R* interval which was followed by a normal *QRS* was 1.48 sec., equivalent to a rate of 40.4 beats per minute. All beats at faster rates had normal *QRS* complexes. The shortest *R–R* interval giving rise to bundle branch block was 1.49 sec., equivalent to a cardiac rate of 40.3 per minute, and here the *QRS* complex was that of lesser degree of bundle branch block.

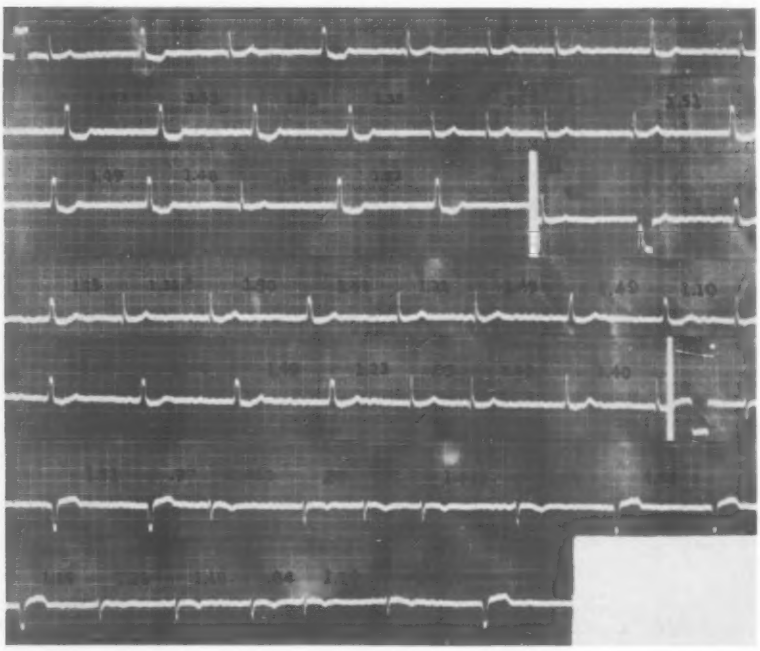

FIG. 5.—Case 2. Leads I, II, and III. Aberrant *QRS* forms lack the small initial deflection, are wider and slurred; the *R–T* segment is displaced. The *QRS* intervals vary from 0.07 sec. in the normal type to 0.12 sec. in some of the aberrant forms.

**Discussion.** The above 2 cases represent conditions of unstable conduction in the branches of the bundle of His. Frequently the equilibrium between normal and abnormal conduction became so delicate that it was disturbed by such subtle alterations as a change in the cardiac rate of only one beat or at times of even a fraction of a beat per minute. This delicate equilibrium was present when the heart was beating at a certain rate level. At this critical rate an

* The belief that these alterations in the *QRS–T* complex are due to a disturbance in the left (or right) bundle branch or their primary branches is assumed[15] rather than that they are produced by effects upon the more distal Purkinje system. This, however, is immaterial to the matter under discussion.

increase in the cardiac rate of only one beat per minute in Case 1, and, in Case 2 where the rate was quite slow, a decrease in rate of one beat per minute, was sufficient to block conduction in a bundle branch. The critical rate varied on different days. At different times in Case 1 it was 65, 71, 72, and 75 with block as these rates were exceeded. In Case 2 a record indicated that when the rate was 40.4 per minute or faster the conduction was normal and when the rate was 40.26 per minute or slower there was block.

The change from the normal to block or the reverse usually took place within the period of one heart cycle. Occasionally, however, the change to block was more gradual with at least one or two intermediary complexes of lesser block simulating the Wenckebach type. This type of bundle branch block with transitional complexes has been produced experimentally by varying the pressure with the blunt edge of a knife on the bundle or main branch.[18,19] Its existence in human cases, however, is rare. An explanation given for this rarity is that the difference between normal conduction and complete bundle branch block is usually only from .04 second to .05 second, leaving little room for transitional stages of partial bundle branch block.[21] In the 2 cases described above the small, gradual variations in rate occurring at times were adequate to bring out these transitional forms.

Digitalis was not taken by either patient up to the time of the observations described.

The pathologic anatomy of the unstable state of conduction may be of any type which involves the branches of the bundle of His or the bundle itself. Congenital septal defects, rheumatic syphilitic or other types of inflammatory diseases, and primary vascular changes, either acute or chronic, involving the arteries to the bundle and its main divisions, are possible causes. Vascular disease is the most common etiologic factor and was considered the cause in the 2 cases described above. The lesion may be a small local one catching a main bundle branch or it may be diffuse myocardial damage with diffuse involvement of the bundle branch system, as found in the majority of cases of chronic bundle branch block by Master and his associates.[13] The second patient who had moderate enlargement of the heart and cardiac failure was most likely one of the diffuse type. The first patient had neither enlargement nor much failure so that one could be less certain of the extent of myocardial involvement.

The nature of the state of unstable conduction has been pictured by Carter and Dieuaide[2] who, in referring to conduction in the auricular ventricular bundle, stated: ". . . . a few intact fibers may under favorable circumstances serve to carry on the process normally, while some subtle local circulatory deficiency or a temporary increase in vagal action may result in failure of the few remaining fibers to function."

Repair of the bundles of His when once destroyed probably does not occur (Erlanger).[12b] Any recovery of function therefore is due

to physiologic alterations. Conduction in the bundle branches may be influenced by oxygen,[1] glucose,[14] drugs such as digitalis,[4] quinidine[11] and morphine,[3] and by changes in the cardiac rate.[3,5,8,21,23] Temporary failure of conduction as in the above 2 cases is considered to be due to local functional changes which are the result of fatigue as described by G. C. Robinson.[17a,b]

Unstable bundle branch block would be observed more frequently if at least one lead of the electrocardiogram were taken both in the recumbent position and after the rate has been increased by any measures deemed feasible, such as change in position or exercise. This would apply, of course, particularly to patients in whom disease of the coronary arteries is suspected. The first patient described in this report was referred to the hospital for study because repeated changes in the *QRS* complex were noted in the electrocardiogram taken in the office of the physician (the late Dr. M. A. Rothschild). The patient was in the sitting position. It is likely that, had the electrocardiogram been taken with the patient in the recumbent position when the heart rate was continuously below the critical level, it would have been normal, as was demonstrated later when the patient was in the hospital. Thus, an important aid in the evaluation of the case would have been missed, at least for some time. Doubtless the same situation holds for other cases. In patients with slow cardiac rates, as in Case 2, it would be desirable to take part of the ECG with the patient in the recumbent position after a period of rest, when slower rates obtain. An occasional instance of bundle branch block may be noted during a spontaneous paroxysm of sinus or auricular tachycardia or after auricular premature contractions.[10]

Of interest also is the fact that a symptom may be present at the time of change from one type of conduction to the other. A "tinkling" sensation in the chest was described by the first patient. This was noted several times to coincide with the changes in conduction as observed on watching the movement of the electrocardiographic string shadow. No unusual sensation in the chest was felt by the second patient.

The prognosis and treatment of unstable bundle branch block is essentially that of the underlying disease of the heart. With improvement the bundle branch block may disappear and normal conduction return permanently or for a long time. This occurred in the second case. If the damage to the myocardium is progressive, then permanent block would be expected. Progressive involvement of the right and left bundle branches might produce complete auriculoventricular block.[24]

**Summary and Conclusions.** A state of unstable conduction in the branches of the bundle of His occurs which is closely related to the cardiac rate. A slight change in rate causes a bundle branch block when the heart is beating at a critical rate level. Bundle branch block similarly reverts to normal with slight changes in rate.

Transitions from normal conduction to bundle branch block and the reverse are usually sudden and take place within a single beat. Intermediary stages of lesser block are present at times.

The pathologic anatomy and mechanism of unstable bundle branch block are discussed briefly. Functional changes of fatigue or recovery from fatigue are probably responsible for the fluctuations between conduction and block.

Two cases are described. In one, ventricular conduction, as expressed by the *QRS*, appeared normal when the cardiac rate was below a critical level. Block was present when the rate was faster. In the second case, ventricular conduction was normal when the rate was above a critical level of 40.3 per minute, and block in a bundle branch was present when the rate was slower.

It is advisable at times, when myocardial changes are suspected, to take the ECG at more than one cardiac rate.

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## SUBACUTE BACTERIAL ENDOCARDITIS ON THE RIGHT VENTRICULAR WALL OPPOSITE A VENTRICULAR SEPTUM DEFECT.

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Discussing defects of the interventricular septum (maladie de Roger), Maude Abbott says: " . . . The clinical picture is thus that of absence of symptoms in the presence of distinctive physical signs

in an otherwise normal individual, and the significance of this lesion lies not in the functional effect of the defect, but in the great frequency with which a subacute bacterial endocarditis develops along its margins or on the opposite wall of the right ventricle. . . ."

A rather exhaustive review of the literature revealed an amazing sparsity of cases similar to the one which we are now reporting. We were able to find but 4 such cases, all in older patients than ours. This is also the only case in which the valve leaflets and the chordæ

*A*

were not as yet involved by the endocarditis.[1a,2,3] In a personal communication Maude Abbott[1b] wrote " . . . this is a clear cut example of an infective endocarditis of the wall of the right ventricle opposite a localized defect of the interventricular septum without vegetations elsewhere. It supplies proof of the direction of the current from the left to the right through the defect."

**Report of Case.** J. P., 7-year-old white Italian male child, the fifth of 6 children—all of whom are living and perfectly well. There is no history

of the occurrence of any congenital defect nor of any cardiac lesions in the family as far back as the grandparents. Physical examinations of the parents and siblings were not made. The patient developed normally up to the time of the present illness. He was in the third grade of the public school. His tonsils and adenoids were removed at 6 years due to frequent

*B*

FIG. 1.—*A*, The opened right ventricle showing the interventricular defect as well as the localized patch of endocarditis on the opposite wall (round area just beyond end of rod). Petechial hemorrhages in the myocardium are also readily seen. *B*, More detailed view of defect.

attacks of tonsillitis. His congenital heart-lesion was first noted at 4 months. However, he was entirely symptom-free up to the onset of his present illness.

His illness began on June 17, 1939, and was characterized by malaise, anorexia and slight fever (up to 101.4° F.) followed by drowsiness. On June 20th physical examination revealed an apathetic, listless and obviously

sick child. The temperature was 100.2°, his pulse was 140 and of fair quality. His respirations were regular, not labored and about 30 per minute. There was no cyanosis. Both turbinates were boggy and red and the nares were filled with a somewhat gelatinous mucoid secretion. The throat was only slightly reddened. The teeth were markedly carious. The anterior and posterior cervical lymph nodes were palpably enlarged. His chest had a normal contour, and his lungs were resonant throughout. The heart was enlarged to the left and presented a systolic thrill, felt over the entire precordium, and most marked at the base. A loud continuous to and fro murmur, heard over the entire precordium, was most distinct at the apex, and could also be heard in the neck vessels as well as in the left posterior chest. The spleen was markedly enlarged, extending almost to the level of the iliac crest. The liver was also enlarged, extending to about 2 fingers below the costal margin. No other masses or viscera could be felt. There was no edema of the extremities. Urinalysis was entirely negative. That night his temperature rose to 104.4°. He became somewhat delirious. The following afternoon several scattered areas of ecchymosis were found over the thighs and lower abdomen (these were between 2 and 3 inches in diameter). No petechiæ could be found. A tentative diagnosis of subacute bacterial endocarditis was made. He was admitted to this hospital on June 23. His temperature continued septic (105.6° to 100.2° F.). On June 25, he became somewhat jaundiced. On June 27 the blood culture was positive for streptococcus (alpha). He continued downhill, despite 3 small (160 cc.) transfusions and sulfanilamide treatment. Roentgen rays on June 24, and again on June 26, showed no pulmonary lesions. Repeated urinalyses failed to reveal red blood cells until on July 9 an occasional red cell was noted. There was a slight trace of albumin and occasional white blood cell. Blood counts showed Hgb. from 65% to 50%; red blood cells from 3,270,000 to 2,420,000. White blood cells varied from 18,350 (June 24) to 3,100 (July 1); neutrophils from 80% (June 24) to 95% (July 3). Blood culture was positive on several occasions for alpha streptococcus. The various agglutination tests (typhoid, para-A, and B, *B. abortus*, *B. melitensis*) were all negative. The blood Wassermann test was negative. Blood smear (July 3) showed no abnormal leukocytes, but a marked shift to the left. Red cells show a moderate variation in size and shape; no nucleated reds. Electrocardiogram: moderate left axis deviation, the *QRS* complex of the "M" shape variety, with some thickening and slurring of all the limbs (indicating intraventricular conduction defect). Fluoroscope and Roentgen ray films of the heart showed it to be moderately enlarged, and of the "wooden shoe" shaped type. Petechiæ were first noted on July 4; 2 were under the conjunctiva of the left eye. July 5, several additional petechiæ appeared over the body. He continued rapidly down hill and died July 9, 1939.

**Autopsy** (12 hours postmortem): The arteries showed no atheroma or arteritis. There was no dilatation or hyperplasia of either the pulmonary artery or the aorta. The pulmonary artery was 3 cm. in circumference; the aorta 4½ cm. There was no evidence of collateral circulation. The coronary arteries and veins were normal. The heart was normal in its position. It was moderately hypertrophied in both the right and left sides. It weighed 120 gm. The right auricle measured 3 by 5 cm. and its wall was 1 mm. in thickness; right ventricle was 5 by 6 cm. and its wall was 2 mm. in thickness; left auricle 3 by 4½ cm. and its wall was slightly more than 1 mm. in thickness; left ventricle 5 by 5½ cm. and its wall was 8 mm. thick. The valve rings were moderately enlarged. The mitral valve measured 5.6 cm. and the tricuspid valve 7.8 cm. in circumference. There were no anomalies or vegetations of any of the valve leaflets. The myocardium showed numerous petechial hemorrhages. The interventricular septum had

a smooth punched-out defect in its membranous portion 1 cm. in diameter. This was surrounded by a thick fibrous ring. On the wall of the right ventricle opposite this defect there was a fan-shaped area of endocarditis, 3 cm. by 2 cm. in diameter. This area was covered with about 100 small warty vegetations which were slightly friable but seemed to contain considerable fibrous tissue. Sections from these vegetations showed them to be composed of an amorphous mass of fibrin and blood platelets. In the deeper portions of the vegetations there was beginning organization with fibroblasts, newly-formed blood-vessels and an infiltration of inflammatory cells, mostly neutrophils. Only 1 group of streptococci could be found in these vegetations. There was a complete erosion of the endocardium in these areas.

**Comment.** The endocardium against which an abnormal flow of blood was directed was evidently damaged. This damage favored the implantation of bacteria from the blood stream resulting in the production of a localized endocarditis. The portal of entry of the blood stream infection may very likely have been the carious teeth.

**Summary.** A report is submitted of a case of Roger's disease with subacute bacterial endocarditis. This was localized to an area in the right ventricle opposite the interventricular defect and was apparently caused by the force of the bloodflow, resulting from arteriovenous shunt. This case appears to be unique in medical literature.

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## THE INTRACRANIAL AND PERIPHERAL VASCULAR EFFECTS OF NICOTINIC ACID.*

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One of the conspicuous effects of nicotinic acid† is flushing of the skin. Abramson, Katzenstein, and Senior[1] have demonstrated by means of plethysmographic and skin temperature studies that an

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† Monoethanolamine Nicotinate (Abbott).

increase in bloodflow through the arm, and to a lesser extent through the leg, results from the oral and intravenous administration of nicotinic acid. That an associated dilatation of the cerebral vessels might also occur has led to the hope that the drug might have a usefulness in certain diseases of the brain by increasing the blood supply to the areas involved. Direct evidence that cerebral vasodilatation follows the administration of nicotinic acid has been offered by Moore,[3] who observed an increase in the diameter of the pial vessels in cats. In a few instances in which lumbar puncture was done, this author also noted a rise in spinal fluid pressure during the appearance of the vasodilatation of the skin. Moore reported improvement of subjective and objective symptoms in 5 cases of multiple sclerosis which he treated with nicotinic acid. He concluded that the favorable results seen following such treatment might be in part due to the effect of the increased bloodflow in the brain.

The present study was carried out to compare by indirect evidence the relative vascular effects of nicotinic acid on the brain and the arm. Several passive and coöperative dementia præcox patients were utilized for this study. The nicotinic acid was injected in doses varying from 12.5 to 150 mg. into the basilic vein, the carotid artery, or the brachial artery.

**Peripheral Vascular Effects.** Flushing of the skin beginning in the face and spreading to the neck, chest, abdomen, arms and back occurs within 1 to 2 minutes, reaching its height within several minutes following the intravenous injection of nicotinic acid in doses from 25 to 150 mg. With the larger doses the flushing is very marked. Rarely is it discernible to any degree below the abdomen. When flushing of the face is marked, injection of the conjunctival vessels is sometimes present. Stroking of the flushed skin of the chest or back with the finger-nail produces a red line followed immediately by a white line which lasts for several minutes. Flushing of the skin following intravenous administration of the larger doses disappears within about ½ hour. The blood pressure shows either an insignificant or a slight rise (up to 10 mm. systolic). In one instance following the intrabrachial injection of 100 mg., the blood pressure rose from 140/100 to 180/110, returning to its original level within 7 minutes. The change in pulse rate was either insignificant or slight, in no instance increasing beyond 12 beats per minute.

When the nicotinic acid is injected into the brachial artery in doses varying from 12.5 to 100 mg., flushing of the injected arm occurs within 1 or 2 minutes and is followed quickly, with the larger doses, by flushing of the face and other parts. The skin of the injected arm shows more flushing and is warmer to the touch than that of the opposite arm. With the smaller doses, the flushing may be confined practically entirely to the injected arm. When the drug is injected in doses of from 25 to 150 mg. into the carotid artery,

marked flushing of the face occurs almost immediately, and is soon followed by flushing of the parts usually involved following intravenous administration.

**Intracranial Vascular Effects.** 1. *Effect on the Retinal Vessels.* In no instance following either the smaller or larger dose of nicotinic acid was vasodilatation or vasoconstriction of the retinal vessels observed by ophthalmologic examination.

2. *Cerebrospinal Fluid Pressure.* This was measured in 8 cases, in 6 cases following intravenous injection of 100 mg., and in the other 2 following intravenous injection of 150 mg. There was no significant change in the cerebrospinal fluid pressure either during or for some time after the height of the flushing of the face, which was very marked in all cases. In one instance, in order to discover whether the cerebral vessels respond differently when narcosis is first induced, 1 subject was given 0.75 gm. of sodium amytal by vein. During the resulting deep narcosis, 150 mg. of nicotinic acid was administered by vein. Very marked flushing of the skin occurred. The cerebrospinal fluid pressure, measured for 30 minutes, showed a rise of only 20 mm. of water.

3. *Arterio-jugular and Arterio-basilic Differences in Oxygen Content.* These were compared following intravenous administration of 100 to 150 mg. of nicotinic acid in 4 cases, and in 5 cases following intracarotid administration of 50 to 150 mg. In 5 other cases the oxygen "uptake" of the arm alone was measured following intrabrachial administration of 25 mg. of the drug.

*Results.* (*a*) Following intravenous administration of the drug, there was a significant diminished arterio-jugular difference in oxygen content in 1 subject. By contrast, a moderate to marked diminished arterio-basilic difference in oxygen content occurred in 3 of the 4 subjects (Table 1).

TABLE 1.—ARTERIO-JUGULAR (A–J) AND ARTERIO-BASILIC (A–B) DIFFERENCES IN OXYGEN CONTENT (VOL. %) FOLLOWING INTRAVENOUS ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE.

| Experiment No. | Dose (mg.). | Before injection. | | Height of reaction. | |
|---|---|---|---|---|---|
| | | A–J. | A–B. | A–J. | A–B. |
| 1 | 100 | 8.0 | 7.4 | 7.2 | 2.5 |
| 2 | 100 | 7.3 | 7.2 | 10.5 | 8.7 |
| 3 | 150 | 5.3 | 7.3 | 4.3 | 2.3 |
| 4 | 150 | 9.2 | 5.3 | 6.0 | 2.9 |

(*b*) Following intracarotid administration of the drug, no significant change in arterio-jugular difference in oxygen content resulted. In 3 of the 5 instances, however, a moderate to marked diminution in oxygen "uptake" by the arm occurred (Table 2).

(*c*) Following intrabrachial administration of the drug with doses much smaller than those injected into the carotid artery, a very marked diminution in arterio-basilic difference in oxygen content occurred in all 5 subjects (Table 3). Samples of arterial and basilic

blood taken simultaneously from the uninjected arm of 2 of the subjects showed no change in oxygen "uptake."

TABLE 2.—ARTERIO-JUGULAR (A–J) AND ARTERIO-BASILIC (A–B) DIFFERENCES IN OXYGEN CONTENT (VOL. %) FOLLOWING INTRACAROTID ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE.

| Experiment No. | Dose (mg.). | Before injection. | | Height of reaction. | |
|---|---|---|---|---|---|
| | | A–J. | A–B. | A–J. | A–B. |
| 5 | 50 | 6.1 | 8.5 | 5.5 | 6.8 |
| 6 | 150 | 3.5 | 4.5 | 4.8 | 6.2 |
| 7 | 50 | 5.5 | 4.1 | 5.5 | 2.7 |
| 8 | 50 | 4.9 | 4.6 | 4.0 | 1.9 |
| 14 | 50 | 4.4 | 4.0 | 4.0 | 2.9 |

TABLE 3.—ARTERIO-BASILIC DIFFERENCES (A–B) IN OXYGEN CONTENT (VOL. %) IN INJECTED AND UNINJECTED ARM FOLLOWING INTRABRACHIAL ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE.

| Experiment No. | Dose (mg.). | Injected arm. | | Uninjected arm. | |
|---|---|---|---|---|---|
| | | Before injection. | Height of reaction. | Before injection. | Height of reaction. |
| 9 | 25 | 8.2 | 1.0 | 8.4 | 8.4 |
| 10 | 25 | 7.5 | 1.5 | | |
| 11 | 25 | 5.4 | 1.9 | 8.4 | 10.1 |
| 12 | 25 | 6.6 | 2.6 | | |
| 13 | 50 | 8.9 | 1.7 | | |

**Effect of Nicotinic Acid on Artificially Produced Raynaud's Syndrome.** In previous experiments, Myerson, Loman, Rinkel and Lesses[4] demonstrated that a Raynaud attack can be simulated following intrabrachial administration of epinephrine in very small concentrations (0.001 to 0.0001 mg.). With doses of 0.01 mg. of this drug a very severe attack is produced. The pallor of the arm and hand following the latter dose lasts about 15 minutes before it begins to wear off.

In 2 subjects such an attack was produced by injecting 0.01 mg. of epinephrine into the brachial artery. At the height of the reaction, which began about 2 minutes later, 25 and 50 mg. of nicotinic acid, respectively, was administered into the artery. Within ½ to 1 minute the pallor began to be superseded by flushing occurring, first, in the forearm, then in the palm, and finally in the fingers. Within 10 minutes in the first case and within 15 minutes in the second, all the pallor had been replaced by flushing. In 2 other subjects nicotinic acid in doses of 25 and 50 mg. was given before the epinephrine (0.01 mg.), both drugs being given by intrabrachial route. Only slight pallor was produced in each subject, lasting about 5 minutes.

**Contrast Between Nicotinic Acid and Some Parasympathomimetic Drugs.** In previous work Myerson, Rinkel, Loman and Myerson[5] demonstrated that prostigmin has a powerful synergistic action with acetylcholine, particularly with acetyl-beta-methylcholine chloride, and that atropine completely blocks the action of the above two cholines. Nicotinic acid, however, is not synergistic with prostigmin,

nor is it antagonized by atropine, at least in respect to vasodilatation. On the other hand, acetylcholine and acetyl-beta-methylcholine chloride are less effective in overcoming the Raynaud-like attack produced by epinephrine than is nicotinic acid.[5]

**Discussion.** That nicotinic acid is a relatively ineffective cerebral vasodilator appears to be indicated by the following: 1, it fails to influence the cerebrospinal fluid pressure; 2, it does not dilate the retinal vessels (comparable to the pial vessels); and 3, probably most significant, it changes only slightly the arterio-jugular difference in oxygen content.

The fact that the cerebrospinal fluid pressure does not change indicates either that the pial vessels do not alter in diameter, or that the cerebral venous pressure does not increase. It is possible, however, for the bloodflow in the intracerebral arterioles and capillaries to increase without pial vasodilatation or an increase in venous pressure, so that the spinal fluid pressure does not change. But under such conditions one should expect a diminished arterio-jugular difference in oxygen content. The fact that this occurs only occasionally, or in much less degree than that observed in the arm, strongly suggests the relative ineffectiveness of nicotinic acid as a cerebral vasodilator. This contrast of vascular effect in the brain and arm is particularly evident when the drug is administered by brachial and carotid routes.

Other drugs, such as histamine and acetylcholine, have been observed to produce dilatation of the pial vessels with a coincident rise in spinal fluid pressure. In our experience no significant or regular change in arterio-jugular difference in oxygen content occurs at the height of the reaction produced by these and other vasodilator drugs.[2] Thus, feeble dilatation of the intracerebral vessels may be associated with a relatively strong dilatation of the pial vessels.

The theory, that when the face flushes the brain flushes, is not borne out by these studies. It is more accurate to state that both areas probably do not flush to the same degree or that flushing of the face is not necessarily associated with flushing of the brain. The obvious resistance of the cerebral vessels to changes in bloodflow following the administration of nicotinic acid and other common vasodilator drugs suggests the probability that attempts to affect impaired cerebral neurons by such means will fail. Whether the physiologic demands of neurons damaged by disease processes can be supplied by increasing the cerebral bloodflow is in itself very questionable.

On the other hand, because of its marked peripheral vasodilating action, nicotinic acid may have a possible clinical usefulness in peripheral vascular conditions in which an increased bloodflow is desired. Such an application of the drug is suggested by the observation that a Raynaud attack, artificially produced, is shortened or overcome by the drug.

**Summary.** Nicotinic acid was administered by intravenous, intrabrachial and intracarotid routes to a group of subjects for the purpose of comparing the cerebral and peripheral (arm) vascular effects. The following observations were made:

1. The cerebrospinal fluid pressure is insignificantly altered.

2. The caliber of the retinal vessels is unchanged.

3. The cerebral bloodflow, using changes in arterio-venous differences in oxygen content as an index, is only slightly increased, while the bloodflow in the arm is usually moderately to markedly increased. This difference in response in the two loci is particularly obvious when the drug is injected into the carotid and brachial arteries.

4. Nicotinic acid shortens the Raynaud-like response produced by epinephrine when both drugs are injected into the brachial artery. This peripheral action of the drug suggests a possible usefulness in Raynaud's and other peripheral vascular diseases.

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## VASOMOTOR DISTURBANCES IN PERIPHERAL NEURITIS.*

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Studies of the cardiovascular manifestations of beri-beri have strongly suggested that the peripheral circulation in the extremities is definitely disturbed and that this disturbance may be an important factor leading to circulatory failure in the disease.[2,6,7] Since peripheral neuritis is one of the common manifestations of beri-beri, there has been some speculation as to whether the disturbances in the peripheral circulation might be due to coexistent involvement of the sympathetic nervous system. Therefore, it was decided to study patients with peripheral neuritis due to dietary deficiency, but

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without circulatory failure, in order to determine if any abnormalities of sympathetic vasomotor function were present.

**Methods.** The skin-temperature of the pads of the digits was measured by thermal junctions lightly applied with adhesive tape. Body temperature was measured by a thermal junction inserted 5 cm. above the rectal sphincter. Room temperature was measured by a thermal junction suspended in the air of the room. The galvanometer allowed the detection of changes of 0.1° C.

The room was draught free, and was maintained at as constant a temperature as possible. Plethysmographic measurements of volume and pulse-wave changes in the fingers and toes were recorded optically by the method of Bolton, *et al.*[1] The subject lay lightly covered for 20 to 40 minutes while control observations were made. The body was then warmed with heating pads and blankets, and by immersing one arm to the elbow in water at 45° C. Temperature and plethysmographic measurements were repeated at frequent intervals. When full reflex vasodilatation had been obtained, stimuli were applied which are known to induce, through the mediation of the sympathetic nervous system,[4] brief vasoconstriction in the digits. These stimuli were the following: (*a*) application of ice to the skin; (*b*) pricking with a pin a sensitive skin area; (*c*) startling the subject by making a sudden loud noise; directing the subject (*d*) to take a deep breath, or (*e*) to solve an arithmetical problem. The body was then cooled by removing the blankets and heating pads, and transferring the arm to cool water (20° C.). Again temperature and plethysmographic measurements were taken at frequent intervals.

The patients (Table 1) were selected from the medical wards where their diet and vitamin intake were carefully regulated. Eight patients had "alcoholic" peripheral neuritis; one, peripheral neuritis of pregnancy; and one, peripheral neuritis following disulfanilamide poisoning. Thirty-five tests were carried out on these patients, some of whom were repeatedly tested over periods as long as 4 months. At the conclusion of each test a neurological examination was made.

**Results.** Half of the patients with peripheral neuritis involving the legs also had a disturbance of the sympathetic vasomotor activity in the feet (Table 1). With one exception these were all untreated patients who had tenderness, definite sensory defects, and areflexia in the legs. The circulatory abnormality consisted of decreased vasomotor tonus in the feet. The toes were constantly warmer than the fingers even with the body exposed in the cool room. After warming the body, the temperature of the toes rose slightly or remained unchanged, while the temperature of the fingers rose to or above that of the toes (Chart 1). At this time the plethysmographically recorded vasoconstrictions in response to brief vasoconstrictor stimuli were slight in the toes as compared with the fingers (Fig. 1). On cooling the body the temperature of the toes decreased slightly, while that of the fingers fell more rapidly and reached a lower level (Chart 1).

Both the digital temperature and the plethysmographically recorded volume changes indicated a decreased vasomotor tonus in the feet. In healthy persons we have always found a greater vasomotor tonus in the feet than in the hands. This confirms the

TABLE 1.—DATA ON 10 CASES OF PERIPHERAL NEURITIS BEFORE AND AFTER TREATMENT.

| Name. | Age. | Sex. | Diagnosis. | Period of observation, mos. | Muscle tenderness. | | Inability to walk. | | Muscle weakness and wasting. | | Sensory defects. | | Areflexia. | | Vasomotor disturbances. | | Trophic ulcers. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before treatment. | After treatment. | Before treatment. | After treatment. | Before treatment. | After treatment. | Before treatment. | After treatment. | Before treatment. | After treatment. | Before treatment. | After treatment. | Before treatment. | After treatment. |
| I. B. | 42 | M | "Alcoholic" polyneuritis | 3 | + | 0 | + | 0 | + | 0 | + | + | + | + | ++ | + | + | 0 |
| I. F. | 51 | M | " | 3 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | + | 0 | 0 | 0 |
| J. McK. | 50 | M | " | 2 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | ++ | + | 0 | 0 |
| C. W. | 39 | M | " | 5 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | ++ | + | 0 | 0 |
| T. W. | 32 | F | Polyneuritis of pregnancy | 1½ | + | 0 | + | + | ++ | ++ | * | * | + | + | Not studied | + | 0 | 0 |
| A. B. | 55 | M | "Alcoholic" polyneuritis | 1 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | " | + | 0 | 0 |
| F. M. | 29 | F | " | 18 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | " | 0 | + | 0 |
| J. S. | 48 | M | " | 1 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | " | 0 | 0 | 0 |
| J. K. | 39 | M | " | 1 | + | 0 | + | 0 | 0 | 0 | + | + | + | + | " | 0 | 0 | 0 |
| W. W. | 19 | M | Disulphanilamide intoxication with polyneuritis | 14 | + | 0 | 0 | 0 | + | 0 | 0 | 0 | + | + | " | 0 | 0 | 0 |

observations of others.[3,5] However, we have frequently found a decreased vasomotor tonus in the feet of patients subjected to lumbar

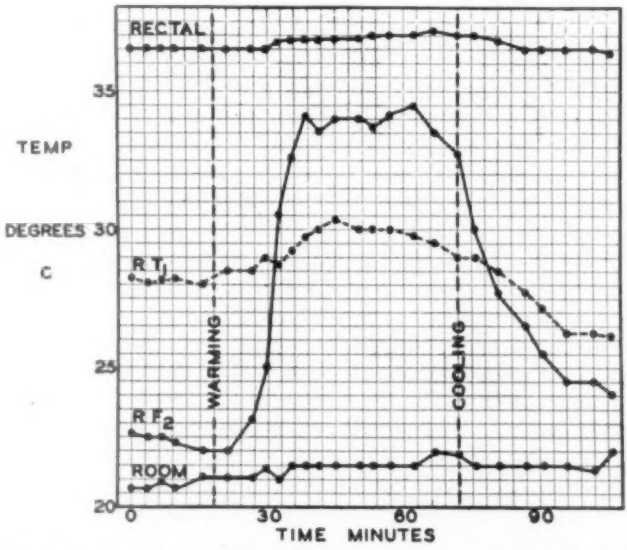


CHART 1.—Rectal temperature, the skin temperature of the right great toe ($R T_1$) and of the right forefinger ($R F_2$), and the room temperature, during a test of the effects of body warming and body cooling on a patient with "alcoholic" peripheral neuritis.

sympathectomy. Indeed, in our patients with peripheral neuritis the measurements of digital temperature and volume changes strongly resembled those found in persons in whom only a partial

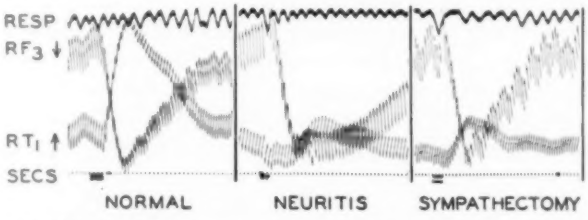


FIG. 1.—Plethysmographic records of vasoconstrictor responses in the right third finger ($R F_3$) and right great toe ($R T_1$) of a normal subject, a patient with "alcoholic" peripheral neuritis, and a patient subjected to bilateral lumbar sympathectomy. The arrow indicates the direction of decrease in volume of the digit. The top tracing shows respiration (Resp.) with the down stroke for inspiration. At the signal (below the seconds marks), ice was applied to the skin of the face.

sympathectomy of the feet had been secured by resection of the first and second lumbar sympathetic ganglia (Fig. 1).

One interesting phenomenon encountered in the involved toes was a delay in the vasoconstrictor response which appeared 7 to 10 seconds after the stimulus, instead of the normal 3 to 5 seconds (Fig. 1). This was found in 3 patients. We have never seen a response as much delayed in normal subjects, or in patients suffering from other diseases.

Three patients were placed on vitamin free (pellagra-producing) diets as soon as they were admitted to the hospital. On this regimen the polyneuritis failed to improve, and the vasomotor paresis became more complete. When thiamin chloride, 50 mg. daily, was administered parenterally, there was an improvement of the vasomotor disorder within 2 weeks, though there was not a return to normal. After this initial improvement, progress was slow and was not apparently accelerated by a diet rich in all vitamins.

The vasomotor disturbance seemed to improve more rapidly than the sensory-motor abnormalities with the exception of muscular tenderness. For example, 1 patient (I. F.) was retested after 2 months of high vitamin therapy at home. At this time the vasomotor responses had returned to normal. The sensory-motor signs, however, were unchanged. The fact that the vasomotor disorder seemed to improve faster after treatment than the sensory-motor disturbance may explain why the former was often not found in patients who had been treated for prolonged periods but still had sensory-motor signs.

One patient (F. M.), seen for the first time after prolonged dietary therapy, still had almost complete loss of sensation in the feet and lower legs. She had no vasomotor hypotonus in the feet. On the contrary, the feet and lower legs were blue and cold. On warming the body, the temperature of the toes rose promptly, and the plethysmographically recorded vasoconstrictor responses were normal except for a delay of the type mentioned above. The patient suffered from "trophic" ulcers on both third toes. For this reason, and against our advice, she was subjected to a unilateral lumbar sympathectomy. After the operation the sympathectomized foot became warm and pink, showing that the sympathetic nervous system had formerly been active. The ulcer, however, showed no greater tendency to heal on this side than on the opposite, cool, unsympathectomized side. This case demonstrates the fact that there was no correlation between the severity of the sensory loss and the vasomotor hypotonus.

That there was no correlation between the degree of motor weakness and the vasomotor disturbance is illustrated by the findings in the patient with polyneuritis of pregnancy. She had a most severe motor paralysis of the lower legs with only slight sensory defects. There was no more than a minimal vasomotor disturbance.

Two of the patients had "trophic" ulcers on the toes. These ulcers were observed in a patient with vasomotor hypotonus and warm feet, and in the patient, cited above, with cold feet. Both

patients had severe sensory loss. This suggests that the ulcerations were due to the sensory defect and not to the vasomotor disorder.

**Discussion.** The finding of a vasomotor disturbance in the feet of patients suffering from peripheral neuritis of the legs, associated with vitamin deficiency, was too frequent to be coincidental. The combination suggested that the vasomotor and sensory-motor abnormalities might have a common pathogenesis. Since the vasomotor disturbances resembled those found in partially sympathectomized limbs, the likely explanation is that these vasomotor disturbances are due to involvement of the sympathetic nerves, just as the sensory-motor signs are due to involvement of the sensory-motor nerves.

It would appear that part of the vasomotor disturbance in these patients was not due to an anatomic defect, since it subsided within 2 weeks of instituting therapy. However, the residual abnormality was either structural or, if functional, only slowly reversible, since a complete return to normal occurred either very slowly or not at all. The evidence indicates that during therapy the recovery was more rapid in the vasomotor than in the sensory-motor system.

One interesting vasomotor abnormality peculiar, so far as we know, to these cases was the much delayed vasoconstriction in the involved toes in response to appropriate stimulation. The reason for this delay is not apparent. We have not observed it in patients after partial or complete sympathectomy.

**Summary.** Disturbance of the vasomotor reactions in the feet was frequently found in untreated patients who had peripheral neuritis of the legs. The disturbance was characterized by a decrease in the vasomotor tonus of the feet, resembling that found after incomplete sympathectomy. A delayed response to vasoconstrictor stimuli was also found in the toes of some of the patients.

There was no rigid relationship between the degree of vasomotor disturbance and the loss of sensation or muscular power. In general, the more severe cases of peripheral neuritis were the ones with vasomotor abnormalities.

Definite improvement in the vasomotor disturbance occurred within 2 weeks of instituting appropriate treatment. However, a complete return to normal vasomotor function required a longer period of therapy.

This investigation was conducted with the technical assistance of Miss Sara B. Merritt, B.S. The authors are indebted to Dr. Alan Bernstein for granting permission to include in this paper observations on one of his patients.

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# BLOOD AND URINE CHLORIDES IN 22 CASES WITH DIABETES INSIPIDUS.

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Patients with diabetes insipidus drink large quantities of water and pass a great deal of urine, often amounting to 10 or more liters per day. If the polyuria of diabetes insipidus is regarded as a diuresis, and I believe that it may be, one would expect to find an increased excretion of sodium chloride in the urine and a decreased serum chloride level, for the reason that diuretics cause an increased excretion of salt along with the increased volume of urine. There are differences of opinion with regard to the serum chloride level and the chloride excretion in the urine in diabetes insipidus. Some investigators have reported hyperchloremia and hypochloremia, hyperchloruria and hypochloruria. Different results, too, have been reported on the effect of pituitrin on the serum and urine chlorides in this disease. Since such variable impressions have been based largely on rare cases, a study was made of the chloride content of the serum and urine in a group of 22 patients over a period of 5 years. In addition, it appeared of interest to determine whether pituitrin, an antidiuretic, would alter the chloride findings. This paper reports the results, which are consistent, of the total chlorides in the serum of 22 patients with diabetes insipidus and, in addition, the total sodium chloride excretion in 2 of these individuals.

There has been considerable interest in chlorides in relation to diabetes insipidus for many years. As far back as 1872, Neubauer and Vogel[11] found an increased chloride excretion in a patient with diabetes insipidus and on one day it reached the enormous amount of 29 gm. Oppenheim[12] obtained a total of 20 to 30 gm. of sodium chloride in the daily urine of 4 cases. There was a marked salt hunger and when the salt intake was reduced, the sodium chloride excretion was less, although the volume of urine was unchanged. The salt had no diuretic effect. More recently, however, it has been shown by Fitz,[5] Rosenbloom and Price[15] and Curtis[4] that the output of sodium chloride in diabetes insipidus was normal; but increasing the salt in the diet increased the total volume of urine in order to get rid of the excess salt. Curtis[4] also observed that under water restriction with salt feeding, the kidneys were able to concentrate both chlorides and solids. Swan[17] suggested as the result of his experiments that the changes in water metabolism in diabetes insipidus are secondary to changes in chloride metabolism while Peters[13] reported that small amounts of salt are swept out by the flow of water. On the other hand, because of the varying results that Veil[20] obtained with serum and urine chlorides in 4 cases, he

classified diabetes insipidus into the hyperchloremic-hypochloruric and the hypochloremic-hyperchloruric types.

Hyperchloremia in untreated diabetes insipidus has also been reported by Rabinowitch,[14] Curtis,[4] Butler and associates[3] and by Talbot and associates.[18] Some of these authors found that the blood chlorides decreased following pituitrin administration. That pituitrin stimulated and increased the total chloride excretion in the urine, while the diabetes insipidus was relieved has been observed by von den Velden,[19] Williams,[23] Rabinowitch[14] and by Butler, Harper and Carey.[3]

In contrast, there have been studies on this disease which indicated that the blood chloride concentration was normal or low and that the excretion of salt was not affected or was decreased by pituitrin administration. Blumgart,[2] Weir,[21] White and Findley,[22] and Winter, Ingram and Gross[24] observed normal blood or serum chloride levels which were not appreciably altered by pituitrin therapy. In addition, White and Findley[22] and Smith and MacKay[16] noted that pituitrin did not affect the total urine chloride excretion while Weir[21] noted a distinct drop in it. Mainzer[9] found a very low serum chloride in 4 cases of untreated diabetes insipidus and in 2 cases the serum chloride, determined again after pituitrin therapy, rose to normal.

**Procedure.** The patients studied were ambulatory and consisted of 15 males and 7 females who have had diabetes insipidus for a number of years. Their ages ranged from 12 to 67 years of age, although most of them were below 25 years. Their salt intake appeared to be that of the usual person and they had no craving for it. The diets were the same during the various tests. Most of the patients had a daily urine output of about 10 liters without treatment and a normal urine volume with sufficient pituitrin therapy. The urine examinations were normal.

The serum chloride was determined on one or more occasions in 22 patients without the administration of pituitrin. During these tests the fluids were taken as desired and usually ranged from 8 to 14 liters. In 15 of these patients, the pituitrin was omitted for from 3 to 10 days before the tests were made, whereas in 7 cases no pituitrin was taken for 2 months to several years previously. The serum chloride was tested again in 11 cases after the patients had pituitrin therapy for a period of time and when they were well controlled with the drug. Fluids were taken as desired and the amounts were within the normal range.

The total excretion of chlorides in the urine in 2 patients was determined daily for 36 and 18 days respectively in the hospital. They were on a constant house diet which contained about 200 gm. of carbohydrates, 90 gm. of fat and 90 gm. of protein. In the first case, the salt in the diet was calculated daily and sodium chloride was added to make the total sodium chloride intake exactly 10 gm. daily, while in the second case the salt intake was approximately 10 gm. daily. The urinary chloride is expressed as sodium chloride in the charts so that the excretion of salt may be compared more easily with its intake. The studies were made with and without pituitrin therapy and in addition, the serum chloride was determined daily or on alternate days.

**Serum Chloride Results.** The results of the serum chloride findings* (Tables 1 and 2) were consistent and did not show the variations recorded by observers already mentioned. The chloride concentrations in all of the cases came within the normal range, regardless of whether the patient had omitted pituitrin for only a few days or whether the patient had not been treated with pituitrin for several years and excreted gallons of urine daily during that period. However, in 2 cases the serum chloride may be considered slightly elevated, being 412 and 421 mg. per 100 cc. serum. The administration of pituitrin did not alter the results appreciably because the serum chloride concentrations were only a few milligrams above or below those levels when no pituitrin was taken. The diuretic effect of the diabetes insipidus and the antidiuretic of pituitrin did not affect the chlorides in these cases. The chloride determinations were repeated on several occasions in most of the cases, but since the results were much the same, only single determinations are reported in the tables. The serum chloride determined daily or on alternate days will be discussed with the urinary chloride.

TABLE 1.—SERUM CHLORIDE IN 22 PATIENTS WITH DIABETES INSIPIDUS WITH AND WITHOUT PITUITRIN ADMINISTRATION.

| Case No. | No pituitrin. Serum chloride. Mg. per 100 cc. | Pituitrin. Serum chloride. Mg. per 100 cc. | Case No. | No pituitrin. Serum chloride. Mg. per 100 cc. |
|---|---|---|---|---|
| 1 | 388 | 394 | 12 | 325 |
| 2 | 349 | 335 | 13 | 361 |
| 3 | 347 | 360 | 14 | 421 |
| 4 | 343 | 360 | 15 | 349 |
| 5 | 349 | 338 | 16 | 374 |
| 6 | 364 | 364 | 17 | 347 |
| 7 | 412 | 370 | 18 | 357 |
| 8 | 340 | 358 | 19 | 344 |
| 9 | 364 | 370 | 20 | 358 |
| 10 | 329 | 355 | 21 | 375 |
| 11 | 392 | 395 | 22 | 368 |

TABLE 2.—SERUM CHLORIDE IN 7 PATIENTS WITH DIABETES INSIPIDUS WHO HAD NO PITUITRIN FOR A LONG TIME.

| Case No. | Serum chloride, mg. per 100 cc. | Daily fluid intake, liters. | Period without pituitrin. |
|---|---|---|---|
| 4 | 343 | 10–14 | 2 months |
| 8 | 340 | 8–11 | Several years |
| 17 | 347 | 10 | Several years |
| 18 | 357 | 7–10 | Several years |
| 19 | 344 | 7–9 | 1 year |
| 20 | 358 | 4–5 | 1 year |
| 21 | 375 | 8–10 | 6 months |

**Total Chloride in Urine.** In the first case, the total excretion of chloride† in the urine was determined daily for 28 days on one ad-

* The chlorides in terms of milliequivalents per liter may be obtained by dividing the mg. Cl% by 3.55, and the gm. NaCl per liter by 0.0585.

† See Footnote on previous page.

mission to the hospital and the results are shown in Chart 1. This case took exactly 10 gm. of sodium chloride daily which included the amount in the food and the added salt. The observations were made for the first 13 days with pituitrin therapy and the average sodium chloride excretion was 9.7 gm. daily, the daily range being 6.7 to 12 gm. During the next 9 days no pituitrin was given and the daily average sodium chloride excretion was 9.1 gm. with a range of from 6.7 to 11.2 gm. During the last 6 days pituitrin was

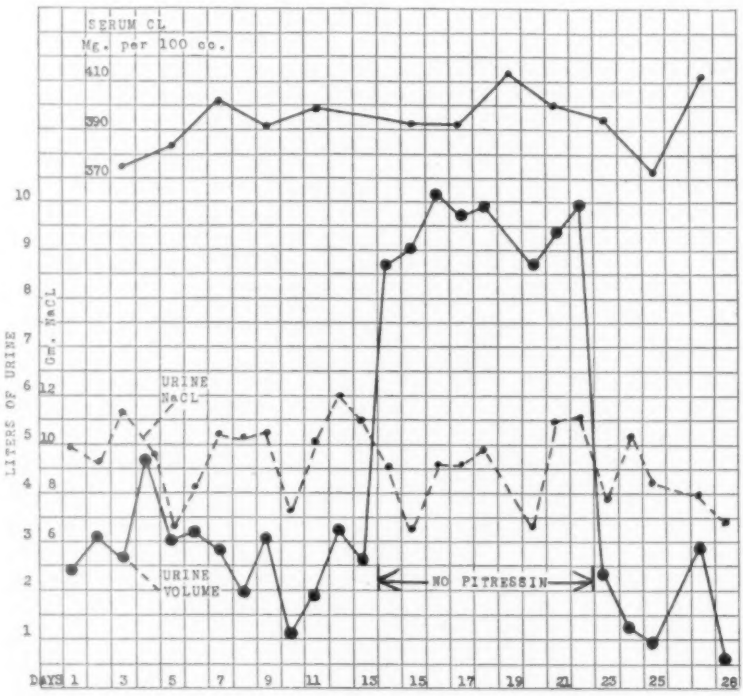


CHART 1.—Daily NaCl excretion and urine output and serum chloride in a patient with diabetes insipidus with and without pituitrin therapy. Diet was constant and contained exactly 10 gm. salt daily. Pitressin 1 cc. was injected every 6 hours. Case 1.

injected again and the average sodium chloride excretion was 8.3 gm. daily, with a range of from 6.8 to 10.4 gm. The serum chloride level showed some slight daily variations whether or not pituitrin was given.

This patient was readmitted to the hospital a month later to observe the effect of restricting the fluid intake on the blood and urine chloride. His sodium chloride intake was exactly 10 gm. daily. The chlorides were determined for 8 days. For the first 4 days pituitrin was administered and the patient took as much fluids as

desired. On the fifth day, pituitrin was omitted and the fluid intake was limited to 3200 cc. and the urine volume was 6050 cc. As the result, he lost approximately 3 kilos in weight and developed such a terrific thirst that he was unable to restrict the fluid intake any longer. The temperature was unaffected. Subsequently, he was given for the next 3 days fluids as desired without pituitrin. The results of this experiment are illustrated in Chart 2. As can be seen here, the serum chloride concentration and the excretion of salt in the urine showed no significant variation during the 8 days of ob-

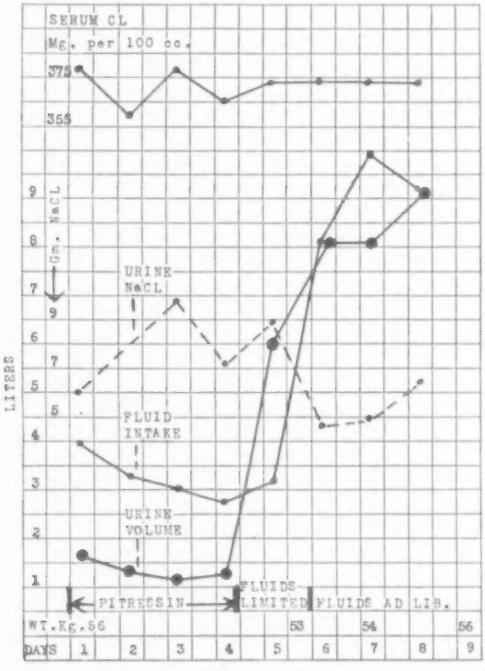


CHART 2.—Effect of restricting the fluid intake without pitressin for 1 day on the NaCl excretion and on the serum chloride in Case 2 with diabetes insipidus. Diet contained exactly 10 gm. salt daily. Pitressin 1 cc. was injected every 8 hours.

servation, regardless of the volume of urine. This was especially true on the day when the fluid intake was restricted which resulted in a considerable loss of weight.

In the second case, the total excretion of chloride in the urine was determined for 18 days when the diet contained approximately 10 gm. of salt daily. The patient had omitted pituitrin and the urine volume was high for a week before admission to the hospital when the studies were commenced. Here the observations were made during the first 5 days without pituitrin therapy, during the

next 10 days with pituitrin injection and finally during the last 3 days again without pituitrin. The daily urine volume was about 13 liters without pituitrin and about 2 liters with pituitrin therapy. In this case, too, there was considerable variation in the daily excretion of salt during the various periods of observations. As the results are so much like those observed in the first case they are not presented in detail here.

A third case of severe diabetes insipidus, observed in the hospital some years ago, was of unusual interest. His daily volume of urine usually ranged from 32,000 to 37,000 cc., although on 1 day the output rose to almost 40,000 cc. His total urinary chloride expressed as sodium chloride was found to be 12.1 gm. during one 24-hour period when the urine was 25,760 cc. This shows that salt is not swept out by the large flow of urine.

**Comment.** The results of this investigation were interesting because they were consistent and because no changes from the normal were found in the serum chloride concentration in this large group of patients even though large volumes of urine were voided over a long period of time which in some cases was several years. The chloride in the spinal fluid determined in 10 of these patients has already been reported[1] as normal. The daily chloride excretion in the urine, too, was normal, in spite of the fact that the urine volume in 1 case was as high as 25,760 cc. and that in another case the fluid intake was restricted to 3200 cc. for 1 day, where his usual intake is about 10 liters daily without treatment. Pituitrin administration did not appear to produce any significant chloride changes in the blood or urine of these patients. If anything, this drug decreased the salt excretion. These results are in contrast to those in which there were found in diabetes insipidus abnormal changes in the blood chloride concentration and a diminished salt excretion which was stimulated by pituitrin administration. Even in normal persons, Manchester[9] and Smith and MacKay[16] noted that posterior pituitary extracts produced a large increase in the sodium and chloride excretion in the urine.

A number of investigators have shown that various diuretics increased markedly the chloride excretion in the urine. Among them are Fulton and associates[6] who found, in addition, in normal dogs that pituitrin inhibited the increased urine volume after novasural but did not prevent the increased chloride excretion. That certain diuretics increase the salt excretion in diabetes insipidus also has been shown. Meyer[10] found in this disease that theocin did not affect the total amount of fluid excreted, but it increased the concentration of sodium chloride in the urine so that during the 24 hours after its administration, the excretion of salt was increased. When theocin was omitted, the chloride output diminished until the normal balance was regained. Fitz[5] gave theocin and theobromin sodium salicylate which alone had no diuretic action in his case, nor

did they increase the total output of sodium chloride. However, when theocin and additional salt were given together, a larger output of chloride was obtained than when no theocin was included. Lindeboom,[7] however, obtained in diabetes insipidus a diuretic effect with salyrgan and an unusually high concentration of salt in the urine for this disease, although the blood chloride concentration showed no significant changes. From my experiments, it appears that the diuretic effect of the diabetes insipidus and the antidiuretic effect of pituitrin do not alter the total serum and urine chlorides in these patients.

These cases show that patients with diabetes insipidus maintain a normal chloride balance when they take an ordinary amount of salt in their diet, notwithstanding the exchange of huge volumes of fluid or the administration of pituitrin. The diuretic effect of diabetes insipidus and the antidiuretic effect of pituitrin did not alter the chloride balance in this disease.

**Summary.** This paper presents a study of the serum chloride concentrations in 22 patients with diabetes insipidus and the total excretion of chloride in the urine of 2 of them.

The serum chloride concentration was found to be normal in these cases, even though some patients had not taken pituitrin for several years. Pituitrin administration did not affect significantly the serum chloride concentration.

The total excretion of chloride in the urine showed some variation from day to day but the results came within the normal range, even though huge volumes of urine were excreted. Pituitrin therapy did not alter the results appreciably. A considerable restriction of the fluid intake in 1 patient for 1 day did not change the serum chloride concentration or the salt excretion in the urine.

Patients with diabetes insipidus taking a normal amount of salt maintain a normal serum and urine chloride balance in spite of the exchange of large volumes of fluid. The diuresis of diabetes insipidus does not affect the serum and urine chlorides like the diuretics in normal people and also the antidiuretic action of pituitrin does not have an opposite action on the chloride balance.

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## ADSORPTION OF SURFACE-ACTIVE SUBSTANCES OF URINES, WITH SPECIAL REFERENCE TO MALIGNANT NEOPLASIA.

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Numerous investigations have dealt with the surface tension of the urine and with physiologic and pathologic changes in the excretion of surface active substances. No definite conclusion could be reached concerning the chemical nature of the substances responsible for the lowering of the urinary surface tension. It can, however, be assumed by reviewing the principal urinary constituents that these surface active substances are represented mainly in the following three categories: 1, bile acids and their salts; 2, fatty acids, their salts and esters; 3, products of protein decomposition, such as peptones, albumoses and oxy-proteic acids. While in one specific condition—icterus—it is known that the low surface tension of the urine is caused by increased excretion of bile acids and their salts,[4] such a chemical identification of the surface active substances has not been possible in various other conditions where lowered surface tension of the urine was encountered. But it seems highly probable that the surface tension of the urine is the result of the excretion of different surface active substances which physiologically and pathologically are subject to changes concerning their quantity and their combination as well.[2,3,17]

In this paper the adsorbability of the urinary surface active substances has been analyzed. The investigations were carried out with the idea that the qualitatively and quantitatively varying combination of surface active substances should find a more instructive expression in their adsorptive behavior than in the surface tension alone. From this viewpoint a large number of urine specimens was investigated, both derived from normal persons and from persons suffering from various diseases. Among the pathologic cases special interest was turned to malignant tumors, as in this condition, not only an increased amount of surface active substances was found in the neoplasms themselves and in the blood serum of the patients, but also several reports indicated changes in the urinary surface tension.

The basic principle of our study was to determine how much of the surface-active substances of a certain urine specimen could be

adsorbed by a constant quantity of an adsorbent. The adsorbability of the surface-active substances in various urines was tested by successive addition of urine to the adsorbent and by determination of the remaining surface tension—indicating the amount of surface-active substances *not* adsorbed by the employed adsorbent. In tentative experiments it was learned that the treatment of the adsorbent with 5-times 10 cc. of urine permitted a sufficient evaluation of the adsorbability of the urinary surface-active substances.

**Procedure.** The stalagmometric method was used for the determination of the surface tension of the urine samples and Norit A in the amount of 100 mg. was employed as adsorbent. The first morning specimens of urines were always used, not less than 3 hours and not later than 6 hours after their collection. In all urine samples tests were made for specific gravity, reaction, and presence of albumin. Specimens exhibiting a pH higher than 8—containing an excess of ammonia—and specimens containing albumin were discarded; likewise urines with a specific gravity lower than 1.010. All urines were filtered and those with a specific gravity higher than 1.010 diluted with distilled water to a specific gravity of 1.010. At least 50 cc. of the urine of 1.010 specific gravity were required for one experiment. To 10 parts of the (diluted) urine 1 part of a buffer was added which consisted of equal parts of M/15 monobasic and M/15 dibasic sodium phosphate. In the urine specimen thus prepared stalagmometry was performed, establishing the surface tension of the original sample (gamma$_0$ or $\gamma_0$). Then 10 cc. of the urine were added to 100 mg. of Norit A in a centrifuging tube, the mixture was vigorously shaken for 1 minute, centrifuged for 10 minutes at 2,000 turns per minute, and the supernatant liquid passed through a small filter for removal of coal particles floating on the surface. Stalagmometry of this filtrate was done, giving the remaining surface tension ($\gamma_1$) of the first 10 cc. of urine, after their adsorption to 100 mg. of Norit A. The same 100 mg. of the adsorbent were now loaded for the second time with 10 cc. of the urine. The mixture was again shaken, centrifuged, run through the same filter and subjected to stalagmometry, furnishing $\gamma_2$. This procedure was repeated 5 times in the same way. The stalagmometry of the fifth sample of 10 cc. of urine, after its adsorption to the original 100 mg. of Norit A, yielded a value of surface tension ($\gamma_5$) which indicated how much of the surface-active substances of this sample could not be adsorbed by the adsorbent after it was successively loaded with 50 cc. of the urine. It is obvious that the adsorbability of the surface-active substances contained in the respective urine sample is decisive for the outcome of the experiment. In the case of a high adsorbability the fifth sample would show only a small amount of surface activity, while a strongly surface-active one would indicate a poor adsorbability. By means of a calculation, given below, this relation was expressed by a ratio depending on the original surface tension of the urine ($\gamma_0$) and the surface tension of the 5th sample ($\gamma_5$). This ratio exhibited certain characteristic variations as may be seen from the tables.

**Technical Details.** The first morning urine specimens were used because of the desire to avoid dilution of the urine by ingestion of water and/or nutritional influences of food. Furthermore, several authors[1,11] found daily fluctuations in the surface tension of urine portions voided by the same person during 24 hours; the highest surface activity, lowest surface tension, respectively, was found in the first morning urine, even independent of the intake of food or drink.[11] Therefore the use of morning specimens should warrant more uniform and comparable conditions than 24-hour specimens. Besides a 24-hour specimen requires the coöperation of the patient, which is not always reliable, and the addition of a preservative.

Stalagmometry was performed not less than 3 hours after collection of the sample because changes occur during this time in the surface tension of the urine until an equilibrium is reached (time factor[6]). The dilution of the urine to the same specific gravity of 1.010 was done for purposes of uniformity. A similar method was used by Schemensky.[13] Objections to this dilution were made by Perryman and Selous[11] and by Hahn,[6] who could not find any direct relationship between specific gravity and surface tension. But these objections are not justified when the stalagmometric method, partly depending on the specific gravity, is employed.

By the addition of the buffer the pH of which was 5.8, the urine pH was brought to an average of 6.5 to 6.8, thus insuring the stability of the reaction. This is highly important because strongly acid and strongly alkaline reaction was found to increase the urinary surface activity,[4,13] and because of the influence of reaction on adsorption. A strongly alkaline reaction—exceeding pH of 8—usually caused by ammoniacal decomposition of the urine—necessitated discarding the sample. In these cases we noted that a high adsorbability of the surface-active substances always prevailed and this was confirmed also in experiments where investigation was first made in the original urine of a pH of 6.8, and then repeated, after alkalinization of the sample with ammonium hydroxide. Likewise albumin-containing specimens were discarded, as the presence of albumin was found to result in a poor adsorbability of the surface-active substances (*cf.* model experiments).

Concerning the choice of charcoal (Norit A) as adsorbent, it must be mentioned that several other substances tested—kaolin, aluminum hydroxide, aluminum silicate, lead acetate and phosphate—did not exhibit any adsorbing capacity for the urinary surface-active substances. Norit A was used because of its defined colloido-chemical structure and high adsorptive quality as compared with other charcoal preparations. The amount of 100 mg. of Norit A was used, since experiments showed this quantity could adsorb practically all the surface-active substances contained in 10 cc. of various urine samples.

The stalagmometric method was employed in this study with full knowledge of the numerous objections raised against its accuracy, as far as the determination of the actual physical value of the surface tension is concerned, and in awareness of the sources of error inherent in this method when used in biological fluids, especially in fluids of a high protein content and viscosity, such as serum.[7] However, the method was considered efficient enough for this study as, on one side, only comparative values of the surface tension were desired and, on the other hand, the above mentioned precautions were taken to warrant the uniformity of the investigated specimens. It might be mentioned here also that in a recent study on the surface tension of the urine in which, simultaneously, the method of capillary rise, stalagmometry and the method of maximum bubble pressure were used, all these methods were found to agree satisfactorily and stalagmometry to give "the most trustworthy data."[5]

The instrument used was the stalagmometer of Traube (Eimer & Amend, No. 28656), holding approximately 4 cc. The instruments were standardized with distilled water. The daily variations of the room temperature were found to be without noticeable influence. The liquid was brought into the instrument by means of a rubber bulb attached to the top of the stalagmometer. The velocity of the falling drops was constant in the determinations performed with liquids of the same specific gravity and of only slightly varying viscosity. The stalagmometer was cleaned prior to determinations, rinsed first with the specimen and frequently thoroughly cleaned with chromic acid. The foam and liquid adhering to the bottom opening were removed with clean filter paper before the determination, thus excluding an important source of error.[9] The drops were counted in the

usual way, the fractions of a drop found by means of the graduations below and above the zero points. Every determination was repeated at least twice and agreement within ±0.1 drop required. The calculation of the surface tension was made according to the equation: $\gamma_1/\gamma_2 = D_1/D_2 \times N_2/N_1$ in which $\gamma_1$ represents the unknown surface tension, $\gamma_2$ the approximate value of the surface tension of water, $D_1$ the density of the unknown, $D_2$ the density of water, $N_1$ the number of drops with the unknown, $N_2$ the number of drops with water.

The evaluation of the experiments was made in the following way: the calculated surface tension of the original (diluted and buffered) specimen was marked $\gamma_0$, the surface tension found in the 5th sample of 10 cc. of urine, after its adsorption to the Norit A, as $\gamma_5$. The latter value indicated how much of the surface-active substances has not been adsorbed by the 100 mg. Norit A at the end of the experiment. The mathematical relation was expressed by the following ratio (R) between the originally present and the not adsorbable surface-active substances:

R = (73.0 (surface tension of water) minus $\gamma_5$) / (73.0 minus $\gamma_0$) .100.

Example: $\gamma_0 - 61.9$, $\gamma_5 - 69.6$. $R = \frac{73.0-69.6}{73.0-61.9} .100 = 30.6$.

Roughly, the ratio of this example could be interpreted as indicating that the 5th treatment of 100 mg. Norit A with 10 cc. of the investigated urine resulted in the failure to adsorb approximately 30% of the originally present surface active substances of the urine specimen used.

TABLE 1.—NORMAL CASES AND VARIOUS DISEASES EXCEPTING MALIGNANCY, ACUTE INFECTION AND TUBERCULOSIS.

| Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_5$ dyn./cm. | R.* | Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_5$ dyn./cm. | R.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Contusion of face | 59.8 | 68.4 | 34.8 | 25 | Fract. fibula | 67.7 | 70.5 | 47.2 |
| 2 | Fract. femur | 61.3 | 69.2 | 32.5 | 26 | Gastritis | 67.7 | 71.7 | 24.5 |
| 3 | Fract. femur | 61.9 | 69.6 | 30.6 | 27 | Fract. pelvis | 67.7 | 71.6 | 26.4 |
| 4 | Coronary sclerosis | 61.9 | 68.1 | 44.1 | 28 | Laceration of leg | 67.7 | 70.8 | 41.5 |
| 5 | Hemorrhoidectomy | 61.9 | 65.2 | 70.3 | 29 | Fract. femur | 67.7 | 72.0 | 18.9 |
| 6 | Contusion of skull | 61.9 | 65.5 | 67.6 | 30 | Normal | 67.9 | 70.9 | 41.1 |
| 7 | Fract. of humerus | 62.5 | 68.8 | 40.0 | 31 | P. appendectomy | 68.1 | 71.6 | 28.6 |
| 8 | Fract. lumbar vert. | 62.9 | 69.2 | 37.6 | 32 | Normal | 68.3 | 71.3 | 36.2 |
| 9 | Fissure ani | 63.5 | 67.3 | 60.0 | 33 | Fract. tibia | 68.4 | 72.0 | 21.7 |
| 10 | Hemorrhoids | 63.9 | 68.1 | 53.8 | 34 | Icterus | 68.6 | 72.1 | 20.5 |
| 11 | Femoral hernia | 64.1 | 69.0 | 44.9 | 35 | Hernia | 68.8 | 72.0 | 23.8 |
| 12 | Fract. tibia | 64.2 | 68.4 | 52.3 | 36 | Arthritis | 68.8 | 72.9 | 2.4 |
| 13 | Prolapsus of rectum | 64.8 | 70.8 | 26.8 | 37 | Frost bites | 68.8 | 72.9 | 2.4 |
| 14 | P. cholecystectomy | 65.5 | 70.8 | 29.3 | 38 | Normal | 68.8 | 72.4 | 14.3 |
| 15 | Liver cirrhosis | 65.5 | 69.7 | 44.0 | 39 | Normal | 69.0 | 70.9 | 52.5 |
| 16 | Fract. femur | 65.9 | 71.6 | 19.7 | 40 | Hypertension | 69.2 | 72.0 | 26.9 |
| 17 | Hemorrhoids | 66.2 | 70.0 | 44.1 | 41 | Fract. femur | 69.6 | 72.0 | 29.4 |
| 18 | Burns | 66.2 | 70.4 | 38.2 | 42 | Fract. femur | 69.6 | 72.0 | 29.4 |
| 19 | Fract. femur | 67.0 | 70.8 | 36.7 | 43 | Varix of groin | 69.6 | 72.4 | 17.6 |
| 20 | Fract. ribs | 67.0 | 70.8 | 36.7 | 44 | Fract. fibula | 69.6 | 72.0 | 29.4 |
| 21 | Fract. tibia | 67.0 | 71.6 | 23.4 | 45 | Cardiac condition | 70.0 | 72.0 | 33.3 |
| 22 | Contusion of back | 67.0 | 70.8 | 36.7 | 46 | Peptic ulcer | 70.1 | 72.5 | 17.2 |
| 23 | Arthritis | 67.3 | 70.8 | 38.6 | 47 | Peptic ulcer | 70.8 | 72.9 | 4.6 |
| 24 | Fract. of hip | 67.3 | 72.0 | 17.5 | | | | | |

* In this and following tables, R = ratio between the originally present and the not adsorbable surface-active substances.

In Tables 1 to 4 118 cases are summarized, the urines of which have been analyzed according to the described procedure. Table 1 contains 47 cases, 21 of which concern urines either of normal persons or of patients with bone fractures or contusions, who also may be regarded as normal as to their metabolic functions. The remaining 26 patients were suffering from various ailments. The surface tension of the (diluted, buffered) urines ranged from 59.8 to 70.8 dyn/cm, the average value being 66.6. In testing the adsorba-

bility of the surface-active substances of these urines, R-values varied between 2.4 to 70.3 (average, 32.9). Of these 46 cases 41 showed R-values lower than 50, and only 6 (approximately 13%) exhibited higher values.

TABLE 2.—CANCER.

| Case No. | Carcinoma of | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. | Case No. | Carcinoma of | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cervix | 53.2 | 57.9 | 76.8 | 28 | Larynx | 65.5 | 70.0 | 68.4 |
| 2 | Lip | 56.8 | 59.6 | 82.7 | 29 | Breast | 65.5 | 68.4 | 64.0 |
| 3 | Tongue | 58.3 | 60.2 | 87.1 | 30 | Cervix | 65.9 | 67.7 | 74.6 |
| 4 | Cervix | 58.8 | 65.5 | 52.8 | 31 | Breast | 65.9 | 69.2 | 53.5 |
| 5 | Cervix | 59.8 | 62.5 | 79.5 | 32 | Gall bladder | 66.2 | 68.8 | 61.8 |
| 6 | Lymphogranuloma | 60.1 | 62.2 | 83.7 | 33 | Larynx | 66.5 | 69.0 | 61.5 |
| 7 | Larynx | 61.0 | 65.2 | 65.0 | 34 | Cervix | 66.5 | 68.6 | 67.7 |
| 8 | Cervix | 61.2 | 63.5 | 83.1 | 35 | Rodent ulcer of face | 66.5 | 71.2 | 27.7 |
| 9 | Lip | 61.6 | 65.9 | 65.7 | 36 | Cervix | 66.5 | 69.0 | 61.5 |
| 10 | Esophagus | 62.5 | 65.9 | 65.7 | 37 | Breast | 66.8 | 69.3 | 59.7 |
| 11 | Esophagus | 62.5 | 64.5 | 81.0 | 38 | Face | 67.0 | 70.0 | 50.0 |
| 12 | Lung | 62.9 | 66.2 | 67.3 | 39 | Rectum | 67.0 | 70.4 | 43.3 |
| 13 | Cervix | 63.2 | 66.5 | 66.3 | 40 | Rectum | 67.3 | 69.6 | 59.7 |
| 14 | Cervix | 63.2 | 66.5 | 66.3 | 41 | Larynx | 67.7 | 70.4 | 49.1 |
| 15 | Esophagus | 63.5 | 66.2 | 71.6 | 42 | Esophagus | 67.7 | 69.7 | 62.3 |
| 16 | Esophagus | 63.5 | 65.9 | 74.7 | 43 | Floor of mouth | 67.7 | 70.8 | 41.5 |
| 17 | Schmincke tumor | 63.9 | 66.5 | 71.4 | 44 | Breast | 68.1 | 70.8 | 44.9 |
| 18 | Tongue | 63.9 | 67.3 | 62.6 | 45 | Floor of mouth | 68.1 | 72.0 | 20.4 |
| 19 | Cervix | 63.9 | 67.7 | 58.2 | 46 | Cervix | 68.4 | 72.9 | 2.2 |
| 20 | Jaw | 63.9 | 67.3 | 62.6 | 47 | Breast | 68.6 | 70.5 | 56.8 |
| 21 | Tongue | 64.2 | 67.7 | 60.2 | 48 | Larynx | 68.8 | 70.8 | 52.4 |
| 22 | Cervix | 64.5 | 67.3 | 67.1 | 49 | Chondrosarcoma of leg | 68.8 | 69.2 | 90.4 |
| 23 | Tongue | 64.5 | 68.1 | 57.6 | 50 | Rectum | 69.2 | 70.4 | 68.4 |
| 24 | Cervix | 64.8 | 68.4 | 56.1 | 51 | Tongue | 69.2 | 72.4 | 15.8 |
| 25 | Stomach | 64.8 | 68.1 | 59.8 | 52 | Cervix | 70.4 | 72.0 | 38.6 |
| 26 | Rectum | 65.1 | 68.6 | 55.1 | 53 | Breast | 70.4 | 72.4 | 23.1 |
| 27 | Sarcoma of maxilla | 65.2 | 67.7 | 68.0 | | | | | |

TABLE 3.—INFECTIONS.

| Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. | Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Erysipelas | 59.0 | 61.3 | 83.6 | 5 | Pneumonia | 65.5 | 66.8 | 82.7 |
| 2 | Pneumonia | 64.2 | 67.7 | 60.2 | 6 | Infect. of thumb | 66.5 | 69.2 | 58.5 |
| 3 | Actinomycosis | 65.2 | 68.8 | 53.8 | 7 | Infect. of hand | 67.7 | 71.2 | 34.0 |
| 4 | Cellulitis of leg | 65.2 | 68.8 | 53.8 | 8 | Empyema | 70.8 | 72.9 | 4.6 |

TABLE 4. TUBERCULOSIS.

| Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. | Case No. | Diagnosis. | Gamma$_0$ dyn./cm. | Gamma$_3$ dyn./cm. | R. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cavernous TB | 53.7 | 63.5 | 49.2 | 6 | Acute pulmon. TB | 66.1 | 70.1 | 44.6 |
| 2 | Acute pulmon. TB | 62.6 | 65.8 | 69.2 | 7 | Cavity in RUL | 66.5 | 70.1 | 44.6 |
| 3 | Bilateral cavities | 64.5 | 68.6 | 51.8 | 8 | Acute TB pneumonia | 66.5 | 69.3 | 56.9 |
| 4 | Acute pulmon. TB | 64.8 | 69.0 | 48.8 | 9 | Cavities in RUL | 66.5 | 70.1 | 44.6 |
| 5 | Fibroid cavernous TB | 65.1 | 68.6 | 55.7 | 10 | TB pneumonia | 66.8 | 69.7 | 53.2 |

TABLE 5.—MODEL EXPERIMENTS.

| Solution, %. | | Gamma$_0$ dyn/cm. | Gamma$_3$ dyn./cm. | R. |
|---|---|---|---|---|
| 0.007 | Sodium oleate | 49.9 | 73.0 | 0.0 |
| 0.035 | Sodium oleate | 27.0 | 68.4 | 10.0 |
| 0.015 | Sodium cholate | 64.5 | 71.3 | 20.0 |
| 0.02 | Sodium cholate | 60.7 | 70.0 | 24.4 |
| 0.04 | Sodium cholate | 57.6 | 64.5 | 55.2 |
| 0.1 | Saponin | 66.2 | 68.4 | 67.6 |
| 0.15 | Saponin | 65.2 | 67.7 | 67.9 |
| 1.0 | Peptone | 59.6 | 60.5 | 93.3 |
| 0.25 | Egg-albumin | 69.2 | 70.4 | 68.4 |

Quite different are the results summarized in Table 2, dealing with 53 cases of malignant tumors. In these urines the surface tension ranges from

53.2 to 70.4 (average, 64.8 dyn/cm). R ranges from 2.2 to 90.4 (average, 59.8). In 43 out of these 53 cases the R-values were found higher than 50, while in 10 (approximately 19%) lower values were observed. Furthermore, 8 cases of acute infections and 10 cases of pulmonary tuberculosis were tested, appearing in Tables 3 and 4, respectively. Although the number of these latter cases is very small, the results are uniform enough: the values for R in 6 out of the 8 infectious cases are above 50 (average, 53.9); while in the tuberculosis urines an average of 51.1 was found for R.

In analyzing these results, the following inferences are made:

1. While the surface tension of the urines derived from patients with malignant neoplasms generally appears to be lower, as expressed in the average value of 64.8 dyn/cm as compared with the respective value of 66.6 dyn/cm obtained in the cases free from malignancy, the surface tension value found in a single case does not present a characteristic means of differentiation between "malignant" and "non-malignant" urines. Taking the value of 66.6 dyn/cm as the "normal" average in our experiments, we find in the "non-malignant" cases (Table 1) 18 out of 47 cases (approximately 39%) exhibiting lower values, whereas in malignant cases (Table 2) 36 out of 53 urines (approximately 68%) belong to this category. To put it simply: among "non-malignant" urines we find 2 out of 5 specimens and in "malignant" cases 2 out of 3 samples which exhibit surface tension values below the "normal" average.

2. Far more characteristic are the findings which were obtained by studying the adsorbability of the urinary surface-active substances, as indicated by the factor R. Assuming 50 as the critical value for R, which, as explained above, indicates that at the end of the experiment 50% of the surface-active substances failed to be adsorbed, we find in the "non-malignant" urines in approximately 87% R-values below 50, and in the "malignant" cases approximately 79% above 50, thus indicating clearly the poorer adsorbability of the surface-active substances contained in the urines of patients afflicted with malignant neoplasms.

3. This difference in the adsorbability of the surface-active substances does not depend on the original surface tension, as may be easily seen from the tables. Comparison of Tables 1 and 2 reveals several identical or similar values of the original surface tension ($\gamma_0$) which are connected with widely varying adsorbability as expressed by R. High adsorbability was observed in urines with very low surface tension and *vice versa*. There is, however, one exception which concerns some "malignant" urines (Table 2, 50 to 53) containing small amounts of surface-active substances, indicated by their high surface tension, and at the same time showing a better adsorbability—within the range of normal values.

4. In the analyzed malignant cases no connection could be established between the extent and severity of the disease on the one side, and between the urinary surface tension and/or the adsorbability on the other side. That is, the results mentioned are not expressions

of the generally impaired condition of the patients, nor can they be attributed to special localizations of the tumors. It seems, however, that the impaired adsorptive quality of the urinary surface-active substances may be more marked in cases where internal tumors existed, as 6 out of the 10 "malignant" urines with normal R-values concerned external tumors, such as face, tongue, and not metastasized breast neoplasms.

5. The few investigated cases of acute infections (Table 3) and of acute pulmonary tuberculosis (Table 4) yielded results very similar to the findings in the malignant neoplasms as regards adsorbability of the surface-active substances. An extremely low adsorbability was observed in 2 cases of pneumonia, while the adsorption in urines of tuberculosis was characterized by values ranging mostly around 50.

Thus a characteristic quality of the surface-active substances concerning their adsorbability was found in the majority of cases of malignant neoplasia and also of acute infections, as compared with the respective behavior of the surface-active substances in urines of normal persons or persons with other diseases than cancer or acute infections. This difference certainly depends on the chemical character of the surface-active substances contained in the different urine categories. However, the most desirable proof for this assumption, the direct chemical analysis, encountered essential difficulties, primarily because all attempts failed to recover the adsorbed surface-active substancet from the adsorbent by elution (*cf.* Bechhold and Reiner[3]). Therefore, another indirect way was chosen, that is, studying in model experiments the adsorptive behavior of several biologically important surface-active substances. As representatives of 4 groups of this kind sodium oleate (fatty acids), sodium cholate (bile acids), saponin, peptone and albumin (protein and protein decomposition products) were analyzed. As outlined above, the surface active-substances of the urine are most probably combined from these groups with the exception of saponin-like substances which may appear in the body and urine as a result of medication only. The results of these experiments, which were performed in the same way as the experiments with urines, are contained in Table 5.

In comparing these results we find the best adsorbability present in sodium oleate solutions as expressed in a R of 10.0, combined with an original surface tension as low as 27.0 dyn/cm. The reverse property—very poor adsorbability—was observed in peptone solutions—R-93.3 ($\gamma_0$-59.6 dyn/cm) and in albumin solutions—R-68.4 ($\gamma_0$-69.2). Between these extremes, cholate maintains a middle position with an adsorption: R-21.0, 24.4, 55.2 for the respective surface tensions of 64.5, 60.7 and 57.6 dyn/cm. A poor adsorption was found for saponin also (R 67.6, 67.9), but, as explained above, saponin does not have special significance in relation to the surface-active substances of the urine.

On the basis of these model experiments, the conclusion appears to be justified that the surface-active substances present in "normal" urines consist, according to their adsorbability, of varying combinations of fatty acids, bile acids, and their salts, respectively. In malignancy, however, and in other urine specimens exhibiting a decreased adsorbability, protein decomposition products, such as peptones, albumoses and oxyproteic acids, must be considered responsible for the lowered surface tension and the diminished adsorbability of the urinary surface-active substances.

A short review of the literature reveals that these results agree very well with previous findings on urinary surface tension, and they also fit satisfactorily into our knowledge of metabolism in neoplasia. With the exception of the direct relation between lowered surface tension and increased bile acid content of the urine in icterus, no definite connection between any pathologic condition and the urinary surface tension could be established.[11] Also, kidney diseases—both of surgical and medical—were shown to be without influence on the urinary surface tension.[10] With regard to the chemical nature of the urinary surface-active substances, Traube and Blumenthal[15] assumed that peptones and other protein decomposition products are to be found among them. Bechhold and Reiner[3] made a similar statement on the basis of their investigations.

Several papers were concerned directly with the urinary surface tension of neoplastic patients. Schemensky[13] mainly studied the effect of acidification of urine on its surface tension. This procedure regularly caused a rise of the surface activity but was more effective in urines of patients with malignant neoplasms. The author found this quality so characteristic that he proposed its diagnostic utilization. While the lowering of the surface tension after acidification of urine was confirmed[4] and in the course of this study similar observations were made, Isaac-Krieger and Friedländer[5] found no diagnostic usefulness of this method. Only 11 of 24 cancer urines showed an "acid effect" exceeding the normal range, whereas "positive" results were obtained in a high percentage of control cases also. From a different angle Adlersberg and Sugar[1] approached this subject by studying the daily fluctuation of the surface tension in urine portions passed within 24 hours. The authors observed in malignancy, as well as in a number of other diseases, such as consumptive tuberculosis, liver diseases and albuminuria, a lesser degree of daily changes in the surface tension than in "normal" cases. This phenomenon was called "iso-stalacturia" and was considered evidence of the presence of protein decomposition products.

On the other hand, it is well known from numerous investigations that the pathologic protein metabolism in malignant neoplasia results in changes of the N-containing substances in the urine. We refer mainly to studies on the "colloidal N" and the oxyproteic acids (Salomon and Saxl[12]). The increased urinary excretion of

these substances in malignancy was studied by several authors (*cf.*[16a]).

This study attempted to clarify the problem insofar as the relation between urinary surface-active substances and excretion of protein decomposition products is concerned. No connection between disease and the value of the urinary surface tension could be established. But in malignancy and in acute infections a characteristic adsorptive quality of the surface active substances was observed. While it is obvious that this quality does not lend itself to diagnostic purposes, it offers some insight into the metabolic processes of these diseases.

In this connection the following possibility may be mentioned purely hypothetically. Protein decomposition products do arise in the body during normal and many other pathologic conditions also. Because of their colloidal character, however, they are stored by the reticulo-endothelial system, as far as they are not destroyed. Both in malignancy and in acute infections, in which conditions we noted the presence of increased amounts of protein decomposition products in the urine, the reticulo-endothelial system was found to be functionally impaired.[14,16b] Therefore a connection between these two phenomena seems to be possible. Adequate animal experiments to clarify this question could not now be performed but will be attempted later if possible.

**Summary.** Studies on the surface tension and on the adsorption of the surface-active substances were performed in 118 urines. These specimens were derived from normal persons and from patients suffering from various diseases. In the majority of the urines of patients afflicted with malignant neoplasms, acute infections, or tuberculosis, a characteristic quality of the urinary surface active substances was observed with regard to their adsorbability. These results were connected with the chemical nature of the surface-active substances, and their significance for the understanding of metabolic processes was discussed.

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# CARCINOMA OF THE PAPILLA OF VATER: CLINICAL FEATURES IN FORTY CASES.

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Carcinoma of the papilla of Vater presents an interesting problem. Ampullary carcinomas are small, give rise to symptoms early in the course of the disease and metastasize late. Timely diagnosis of organic disease in these cases should be possible, because obstruction of the vital common bile duct and pancreatic ducts produces easily recognized symptoms. That the cause of the obstruction is carcinoma of the papilla, however, cannot usually be ascertained until operation or necropsy. Surgical treatment offers cure or palliation.

The 40 cases of carcinoma of the papilla of Vater forming the basis of this study are only a part of the cases of this type which have been recognized surgically at the clinic. We have chosen to review only those 40 in which the location and the carcinomatous character of the lesion were confirmed by surgical exploration and biopsy or by necropsy. Some type of operation was performed in 33 of these 40 cases, but specimens for microscopic study were obtained at operation in only 7. Also, in 33 the diagnosis was confirmed by necropsy.

**Incidence and Material.** Carcinoma in the region of the papilla of Vater is not so rare as one would believe from the relatively few reports in the literature; in fact, it is not uncommon. Cooper and Baggenstoss stated that the lesion can be demonstrated in about 0.2% of all postmortem examinations. Most writers accept 55 years as the average age at which the disease occurs but others reporting series of cases have observed, as we have in this study, that the incidence extends from youth to old age. In this series of 40 cases the youngest patient was 26 years of age, the oldest 67; 27 patients were in the sixth or seventh decades of life. The disease is much more common among men than among women, the ratio varying in different estimates from 2:1 to 6:1. Of the patients concerned in this study 34 were men and 6 were women.

Baggenstoss[1] recently studied, grossly and microscopically, the resected tissue in 28 of the 33 cases herein reported in which necropsy was made. The classic studies of Cohen and Colp,[2] Crohn,[4] and Outerbridge[10] should be mentioned in any review of the subject of carcinoma of ampulla of Vater.

**Clinical Features.** The anatomic arrangement in the region of the papilla or of the ampulla leads naturally to the development of

obstruction of the common bile duct and pancreatic ducts and to the production of symptoms. It is interesting that in the series under discussion the possibility of carcinoma of the ampulla was suggested in only 1 case, before operation, but in 38 the diagnoses indicated that the clinician knew that obstruction of the common bile duct was present (Table 1).

TABLE 1.—VARIOUS PREOPERATIVE DIAGNOSES AND THEIR INCIDENCE IN 40 CASES OF CARCINOMA OF THE PAPILLA OF VATER.

| Diagnosis. | Incidence. |
|---|---|
| Carcinoma of pancreas | 15 |
| Stone in common duct | 9 |
| Obstruction of common duct | 9 |
| Stricture of common duct | 4 |
| Cholecystitis | 2 |
| Cirrhosis of the liver | 1 |
| Hepatogenous jaundice | 1 |
| Intra-abdominal malignant disease | 1 |
| Carcinoma of ampulla | 1 |
| Empyema of gall bladder | 1 |
| Carcinoma of ovary | 1 |
| Duodenal ulcer | 1 |
| Carcinoma of liver | 1 |
| | 47* |

* In 7 cases two diagnoses were made.

Since Musser,[2] in 1889, called attention to the association of symptoms, jaundice has been an accepted feature of carcinoma of the papilla. Through the years the only point of argument has been whether or not the jaundice is intermittent or constant. In this series of 40 cases jaundice was a constant feature, being definitely present in 38 when the patients were admitted to the clinic and developing in the other 2 cases while the patients were under observation. In more than half of the cases jaundice was of a degree sufficient for it to be one of the chief complaints. In 8 cases, jaundice was intermittent, the patients having recovered from one or more attacks in the months or years preceding the final episode. In 32 cases jaundice was constantly present although fluctuating. In a few instances it was said to be non-fluctuating. A mildly fluctuating, slowly progressing jaundice, usually of much less intensity than the progressive icterus of carcinoma of the pancreas, and occurring only once in each case, was the most frequently described type. The greatest period of fluctuating jaundice was 24 months and it is interesting that for long intervals this presenting symptom was unaccompanied by any other disturbance. The longest spell of continuous, non-fluctuating jaundice was 5 months. In cases marked by protracted, fluctuating jaundice, the outstanding symptoms early in the course of the disease were anorexia and gradual loss of weight, whereas pain, nausea and vomiting occurred late. In the smaller group of cases in which the jaundice was non-fluctuating the patients were worse and their course was more rapidly

downhill. Loss of weight and strength was a consistent feature; more than 90% of patients in this group lost weight, 1 patient 60 pounds (27.2 kg.) in 4 months.

Contrary to earlier opinions,[3,7,8a,b,11] carcinoma of the papilla of Vater is not painless. Twenty-four of the 40 patients had experienced pain of some kind, and pain was one of the chief complaints of 16 of the 24 patients. In 11 of these 24 cases the pain may have been at least partially due to a stone that was present in the common duct, but not necessarily so, for as we shall see later, pain similar to that produced by stone occurred in cases without either cholelithiasis or choledocholithiasis (Case 2). The pain was either colicky or mild and continuous. In general, the milder, continuous type of epigastric pain, together with some tenderness in the right upper abdominal quadrant, was the more frequent finding. In 1 case vague abdominal pain had recurred at intervals in the 48 months prior to the onset of the final episode. In an additional 14 cases abdominal pain of greater or lesser severity preceded the final episode of pain or jaundice.

Chills and fever have been reported to be present in from 12 to 33% of cases of carcinoma of the papilla. These symptoms were present in a larger proportion of cases in this series, being described by 22 of the 40 patients. The finding of stone in the common duct at operation in 10 of these 22 cases indicates that the stones had something to do with the chills and fever. Ninety per cent of our patients experienced nausea at some time, and nausea and vomiting accompanied the more severe attacks of pain and even a good proportion of the milder attacks. Pruritus, naturally, was a troublesome symptom in view of the duration of jaundice and the intensity of damage to the liver in many of these cases.

The descriptions given by the patients of behavior of bowel function presented a number of interesting points in addition to the tendency to acholic stools and dark urine. It is particularly interesting that in 10 of the 38 cases in which the color of the stool was described, tarry stools had been noted by the patients, indicating bleeding from the surface of the tumor; the tendency to bleed will be discussed later. Diarrhea was described as being present in 22 cases. The stools were steatorrheal in a small number of cases.

A number of reports of cases are presented in abstract to illustrate various types of jaundice, with and without pain. These reports illustrate clearly that no typical clinical syndrome may be attached to carcinoma of the papilla.

**Painless Intermittent Jaundice.** CASE 1.—A man, aged 50, registered at the clinic April 17, 1935. In December, 1933, he had had an attack of painless jaundice associated with severe pruritus, anorexia, loss of weight and extreme fatigue which had persisted for 3 months. The patient had been able to return to work but did not fully recover his strength. In December, 1934, a similar episode of jaundice had begun with diarrhea. No pain was

present, the jaundice fluctuated in severity, the stools were alternately acholic and pigmented.

Physical examination at the clinic revealed the jaundice to be fairly deep and the liver enlarged. A mass that presented the physical characteristics typical of the distended gall bladder of malignant obstruction was palpated in the right upper abdominal quadrant. The concentration of bilirubin was 14 mg. per 100 cc. of serum; results of the Schmidt test for urobilin in the stools were consistently negative. The activity of lipase in the blood serum in terms of twentieth-normal solution of sodium hydroxide ranged around 2 cc. Diagnosis was made of carcinoma of the head of the pancreas. Exploratory operation disclosed the head of the pancreas to be hard and nodular and the gall bladder to be distended, containing two small stones; cholecystogastrostomy was performed. Necropsy revealed carcinoma of the papilla of Vater.

In the foregoing case the jaundice was not only intermittent but in the last attack fluctuating as well. It is possible that the primary attack of jaundice was intrahepatic in origin and unrelated to the terminal attack. It may be assumed however that the onset of jaundice was the first manifestation of the carcinomatous obstruction of the common bile duct, and that the obstruction subsequently disappeared through ulceration of the neoplasm only to reappear after an interval of 9 months. At the time of admission the distended gall bladder and the persistently negative results of the Schmidt test for urobilin in the stools left no doubt that the jaundice was due to obstruction or that the obstruction was a malignant lesion. The palpable gall bladder and the elevation of lipase in the serum pointed to the pancreas or the papilla as the site of the lesion. Further differential diagnosis being impossible, the painless intermittent jaundice was ascribed to the most frequent cause, and clinical diagnosis was made of carcinoma of the head of the pancreas.

**Painful Intermittent Jaundice.** Case 2.—A woman, aged 48, registered at the clinic Sept. 9, 1933, complaining of abdominal pain which she had had at intervals over a period of 18 months. The first attack had lasted a number of hours, had been associated with chills and fever, and had been followed by jaundice, acholic stools and dark urine that had continued for about 4 days. Seven months later, or 11 months before the patient's admission to the clinic, a seizure of severe colic in the right upper abdominal quadrant, lasting 6 hours, necessitated morphine for relief; this attack likewise was followed by jaundice, chills and fever. The jaundice had persisted 2 months and during this time the patient had repeated attacks of pain, chills and fever. Eight months later, or 3 months before admission a similar attack had begun and had persisted with fluctuating jaundice until registration. On examination it was learned that the patient had lost 28 pounds (12.7 kg.); she was emaciated and deeply jaundiced; the abdomen was distended, the liver enlarged and the palpable gall bladder presented the characteristics of the distended gall bladder of malignant obstruction. The concentration of bilirubin in the serum ranged around 15 mg. per 100 cc. and the van den Bergh reaction was direct. Results of chemical analysis of the stools for bile were consistently negative but small amounts of bile were obtained by the duodenal tube from the duodenal cavity. Exploratory operation revealed ascites, multiple metastatic lesions in the liver and a mass in the region of the head of the pancreas; necropsy disclosed a large carcinoma of the ampulla of Vater.

A more typical story of stone in the common duct could not be written than in the case just reported. The jaundice was painful and was definitely intermittent and obstructive. The degree of obstruction on the patient's admission to the clinic was indicated by the small amount of bile obtained through the duodenal tube and by the negative results of tests for bile in the stools. The palpable mass in the right upper quadrant of the abdomen might have been mistaken for empyema of the gall bladder but its physical characteristics led to the belief that the gall bladder was distended because of malignant obstruction. Stones were not found in either the gall bladder or the common bile duct at operation or at necropsy. There seems little reason for doubting that the carcinoma of the papilla was responsible for the recurring attacks of pain, chills, fever and jaundice.

In many cases of carcinoma of the papilla in which a story of common duct stone is obtained, stones as well as carcinoma are found; when both are present one may wonder, in view of the case just described and of similar cases, whether stone or carcinoma is responsible for the pain.

**Painless Constant Jaundice.** CASE 3.—A man, aged 53, was admitted to the hospital Oct. 17, 1938. Painless jaundice, mild but fluctuating in intensity, had begun in August of that year and had been accompanied by pruritus, light stools and dark urine. The concentration of bilirubin was 8 mg. per 100 cc. of serum; a normal amount of good bile was obtained by duodenal tube. During hospitalization the patient gained weight, his condition improved, concentration of bilirubin dropped to 2.0 mg. per 100 cc. of serum, and the jaundice decreased. It was assumed that the jaundice was probably intrahepatic in origin and the patient was dismissed Nov. 4.

The jaundice did not entirely clear, it continued to fluctuate in depth, and the patient again began to lose weight. At the time of his second admission to the clinic, Apr. 3, 1939, the jaundice was mild, the concentration of bilirubin was 12.0 mg. per 100 cc. of serum, the activity of lipase in the blood serum in terms of twentieth-normal solution of sodium hydroxide was 3 cc. Abdominal examination gave negative results. Duodenal drainage produced a satisfactory amount of bile which appeared normal but contained some old and some fresh blood. Exploratory operation revealed ascites, marked biliary cirrhosis, a distended gall bladder and an ampullary tumor measuring 2 by 1.5 cm. in diameter. Cholecystogastrostomy was performed as a palliative measure. Death occurred 8 months postoperatively.

The obstruction in the foregoing case was incomplete on each of two examinations of the patient at the clinic; a normal amount of good bile was recovered by duodenal tube and the concentration of bilirubin at the highest was between 8 mg. and 12 mg. per 100 cc. of serum. The jaundice was constant but distinctly fluctuating. The apparent patency of the common bile duct, as indicated by the foregoing findings, as well as the general improvement in the patient's condition, justified the tentative diagnosis of intrahepatic jaundice at the first admission. At the time of the second admission the

picture had changed in certain essentials. The increased activity of lipase in the serum pointed definitely to primary or secondary pancreatic involvement and this, together with the blood in the duodenal contents, suggested an ulcerating and bleeding malignant lesion of the pancreas or the papilla. It is interesting that in spite of the partial patency of the common bile duct the gall bladder at surgical exploration was found to be distended.

**Diagnosis.** Carcinomas of the papilla have manifested themselves by combinations of symptoms other than those described: by recurrent pain with chills and fever without jaundice until the terminal attack; by constant, fluctuating jaundice with chills and fever but no pain; by progressive non-fluctuating jaundice alone. In 1 case the anorexia and loss of weight overshadowed all other symptoms. It is clear that the clinical picture cannot be relied on for early diagnosis.

Certain physical and laboratory findings serve to establish the obstructive nature of the jaundice and the malignant character of the obstruction. In 25 of the 40 cases distended gall bladders were palpated; in 6 more cases tremendously distended gall bladders were found at operation. Distention of the gall bladder may occur even when the common bile duct is only partially occluded, as in Case 3, and it is undoubtedly the most important finding encountered in cases of carcinoma of the papilla inasmuch as it points definitely to malignant obstruction, as in Cases 1 and 2. Probably in all, or nearly all, cases the gall bladders are enlarged, but not all the gall bladders are felt on examination, since the palpability of the organ depends on the degree of muscular development and relaxation as well as on obesity. Most curious was the disappearance of the distention of the gall bladder in 4 cases, prior to operation; in 1 case after severe upper abdominal pain the gall bladder literally vanished beneath the examiner's fingers. In this case an ulcerating carcinoma of the ampulla was found, and we believe that disappearance of the distention of the gall bladder is to be explained on the basis of recanalization or ulceration of the carcinoma.

Roentgenologic examination has not proved of great value in diagnosis of carcinoma of the region of the papilla. Of the cases here presented the gall bladders were examined roentgenologically in 10, and it is interesting that in 7 the gall bladder functioned normally in spite of existing jaundice. In 3, the roentgenologic finding of non-functioning gall bladders containing stones served only to confuse the diagnosis. Thirty of the 40 patients were subjected to roentgenologic examination of the stomach and duodenum. This procedure likewise proved to be of little value, the results being negative in 20 cases and showing some type of deformity of the duodenum, interpreted as duodenitis, flattening from extrinsic pressure and duodenal ulcer, in the 10 cases.

In 25 of the 40 cases considerable information of value was obtained by examination of duodenal contents removed through the duodenal tube. Bile was absent in 14 cases, indicating the obstructive nature of the jaundice; blood and bile were present in 3 instances, and blood alone in 8, indicating that the lesion was ulcerating and bleeding. It is important to know that evidence of bleeding was discovered by examining the duodenal contents in 44% of the 25 cases.

Data of considerable value likewise were obtained by chemical examinations of the stools and urine; that the stools were acholic and the urine bile-containing is not sufficient comment. More important was the finding of occult blood in 15 cases other than the 10 in which tarry stools had been noted by the patients. Denechau, Tonguy and Varangot[5] (1931) have called attention to the frequency of occult blood in the stools in carcinoma of the papilla. The tendency for ampullary lesions to bleed is very definite; even fatal hemorrhage has been reported (Halsted,[6] Cooper[3]).

Blood counts not infrequently disclose anemia. Determinations of the concentration of bilirubin evidence the depth of jaundice and when carried out frequently, reveal the fluctuations in depth. In this series the concentration of bilirubin ranged from 1.0 mg. to 28.8 mg. and averaged 14.6 mg. per 100 cc. of serum. The van den Bergh reaction was direct in all cases. The determinations of enzymes in the serum have shown increased activity in approximately 66% of cases; such elevated values however do not often aid in distinguishing among various types of pancreatic disease. Determinations of enzymes in the duodenal content were not carried out to any extent in this series. Various tests of hepatic function have been of little assistance in cases of this type.

**Differential Diagnosis.** Jaundice due to carcinoma of the papilla must be distinguished from jaundice of hepatogenic origin when the duct is patent; that is, when there is bile in the duodenal contents, the gall bladder not palpable and pain is absent. Absence of enzymes from the duodenal contents, and presence of elevated values for amylase and lipase in the serum, and of glycosuria and hyperglycemia, if known to have been absent prior to the onset of the disease, will point to pancreatic involvement and away from a primary intrahepatic disease. Such findings, however, will not denote the nature of the pancreatic disease; gross or occult bleeding is strong evidence of a malignant lesion of the pancreas or of the papilla.

Carcinoma of the papilla must be distinguished from stone in the common bile duct when the jaundice is fluctuating and pain has been, or is, present. If a distended gall bladder characteristic of malignant obstruction is palpated, it may be assumed that malignant disease, with or without stone, is present; but if the gall bladder

is not palpated and the obstruction is incomplete, the malignant character of the lesion may be suspected from the progressive course of the disease and especially if gross or microscopic bleeding is present. Functional tests of the pancreas will denote whether or not the pancreas is involved but will not reveal the character or location of the primary lesion and will not exclude the existence of disease of the biliary tract as well as of pancreatic disease.

Carcinoma of the papilla can be distinguished from carcinoma of the pancreas only with the greatest difficulty. Long continued, fluctuating jaundice together with partial obstruction of the common bile duct and a palpable gall bladder will suggest carcinoma of the papilla but similar clinical pictures are seen in carcinoma of the head of the pancreas. Similarly, blood in the duodenal contents will not serve to distinguish the 2 processes, since bleeding may occur in carcinoma of the head of the pancreas, owing to ulceration into the duodenal wall.

**Comment.** The diagnosis of carcinoma of the papilla is difficult because the disease presents no typical clinical picture and no typical physical findings. It simulates both benign and malignant obstruction and with the exception of occasional cases in which the findings point to hepatogenic jaundice, the jaundice is obviously obstructive and can be corrected by surgical intervention. Even in the presence of jaundice simulating hepatogenic jaundice, careful observation will disclose developments pointing to the obstructive nature of the process. The hope for successful surgical treatment of carcinoma of the papilla lies in the fact that the picture, even in the early course, is typical of organic disease. Increased awareness on the part of the surgeon of the possibility and of the frequency of carcinomatous involvement of the region of the papilla eventually may evolve satisfactory surgical approach to the treatment of these lesions, as described by Whipple.[12,13] Preoperative and postoperative care has advanced sufficiently greatly to reduce the operative mortality. Surgical measures such as cholecystogastrostomy offer much from a palliative standpoint, when removal of the carcinoma is not feasible.

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# AN ANALYSIS OF THE DIABETIC MORBIDITY AND MORTALITY IN A GENERAL HOSPITAL.

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Various statistical analyses attempting to evaluate the changes wrought by the introduction of insulin therapy agree that the life expectancy of the diabetic has greatly increased; that coma and sepsis have greatly decreased as causes of diabetic death; and that the percentage of deaths due to arteriosclerotic complications has not been altered appreciably.

These analyses have concerned themselves with the actual causes of mortality. The amenability to insulin therapy of certain complications has removed these from the mortality column and thus may lead to underestimation of their existence, frequency and importance. The present study, therefore, concerns itself with the morbidity as well as mortality in diabetics. These statistics are published with the view to making the data from an institution with a comparatively large diabetic population available for comparative studies.

One gauge for the estimation of morbidity is a study of the admissions of diabetics to a general hospital. The hospital records of all diabetic patients admitted to this hospital were reviewed for the period from 1933 to 1939. This 7-year period was chosen because it represented approximately 1000 diabetic patients, the exact number being 997. Some of these patients were admitted more than once during this time interval, bringing the total number of admissions to 1164. Of this number of diabetics 436 were males and 661 were females. For comparison, the total of admissions to this hospital, for all causes, in this period of time was 91,100.

An analysis of the age groups of the diabetic patients admitted, reveals the following:

| | | | |
|---|---|---|---|
| 10 years and under | 16 | 41 to 50 years | 202 |
| 11 to 20 years | 39 | 51 to 60 years | 280 |
| 21 to 30 years | 31 | 61 to 70 years | 294 |
| 31 to 40 years | 65 | 71 to 80 years | 70 |

The sudden rise in incidence over the age of 40 parallels the incidence of diabetes by age groups in the general population.

During this 7-year period there were 193 deaths in this group of patients, an approximate mortality rate of 17.5%. One hundred and thirteen postmortem examinations were performed, an average of 58.5%. This relatively high percentage of postmortems is largely due to the interest and coöperation of the house staff.

Tabulation of the discharge diagnoses is given in Table 1. There are certain very definite lessons to be learned from this computation One is that the acute infections still account for a large percentage of admissions of diabetic patients to the hospital. This perhaps may seem strange in view of the effectiveness of modern therapy in controlling the clinical symptomatology of diabetes.

TABLE 1.—DISCHARGE DIAGNOSES.

| Complications. | Times diagnosis was made. |
|---|---|
| *Vascular Disease* | *628* |
| Hypertension | 163 |
| Gangrene | 106 |
| Coronary thrombosis | 89 |
| Congestive heart failure | 81 |
| Retinopathy | 80 |
| Amputations for gangrene | 55 |
| Cerebral thrombosis and hemorrhage | 27 |
| Glomerulonephritis | 15 |
| Pulmonary embolism | 10 |
| Thromboangiitis obliterans | 1 |
| Paroxysmal tachycardia | 1 |
| *Gastro-intestinal* | *146* |
| Gall bladder disease | 82 |
| Cholecystectomy | 24 |
| Peptic ulcer | 18 |
| Cirrhosis of liver | 8 |
| Acute hepatitis | 6 |
| Colitis | 3 |
| Intestinal obstruction | 2 |
| Pancreatic cyst | 2 |
| Gastrectomy | 1 |
| *Genito-urinary Diseases* | *85* |
| Prostatectomy | 25 |
| Cystorectocele | 16 |
| Uremia | 16 |
| Renal calculi | 13 |
| Cystitis | 8 |
| Vesical calculi | 6 |
| Tuberculous kidney | 1 |
| Amyloid kidney | 1 |
| *Hematologic Diseases* | *36* |
| Secondary anemia | 20 |
| Leukemia | 4 |
| Polycythemia | 4 |
| Pernicious anemia | 4 |
| Hodgkin's disease | 2 |
| Agranulocytosis | 1 |
| Gaucher's disease | 1 |
| *Endocrine Disturbances* | *46* |
| Hyperthyroidism | 44 |
| Pheochromocytoma | 1 |
| Cushing's syndrome | 1 |
| *Neoplasms:* | |
| Malignant: | |
| Carcinoma | 63 |
| Benign: | |
| Uterine fibroids | 16 |
| Adenoma of bronchus | 2 |
| Neurofibromatosis | 2 |
| Acoustic neuroma | 1 |
| *Infections* | *407* |
| Abscess | 127 |
| Bronchopneumonia (chiefly terminal) | 70 |
| Sepsis | 33 |
| Tuberculosis | 32 |
| Pyelonephritis | 22 |
| Lobar pneumonia | 21 |
| Acute otitis media and mastoiditis | 20 |
| Acute sinusitis | 17 |
| Appendicitis | 12 |
| Lung abscess | 11 |
| Erysipelas | 10 |
| Acute upper respiratory infection | 10 |
| Thrombophlebitis | 10 |
| Acute pancreatitis | 6 |
| Empyema | 2 |
| Vincent's angina | 2 |
| Meningococcus meningitis | 1 |
| Acute salpingitis | 1 |
| *Coma and Ketosis* | *201* |
| *Allergy:* | |
| Asthma | 8 |
| Angioneurotic edema | 2 |
| *Skin Diseases:* | |
| Psoriasis | 6 |
| Vulvitis | 5 |
| Herpes zoster | 1 |
| *Minor Surgery:* | |
| Foreign body (needle) | 5 |
| Tooth extraction | 5 |
| Fistula in ano | 3 |
| *Neurologic:* | |
| Amyotrophic lateral sclerosis | 1 |
| Myasthenia gravis | 1 |
| Ménière's disease | 2 |
| *Miscellaneous:* | |
| Lues | 33 |
| Cataract operations | 41 |
| Rheumatic heart disease | 18 |
| Fractures | 15 |
| Acute alcoholism | 3 |
| Strangulated hernia | 3 |
| Boeck's sarcoid | 1 |

TABLE 2.—PRINCIPAL CAUSES OF DEATH IN 193 CASES.

| | Without coma. | With coma. |
|---|---|---|
| *Infection:* | | |
| Otitis media purulent acute | | 1 |
| Acute mastoiditis with sepsis | 3 | |
| Mediastinitis | 2 | |
| Carbuncle with sepsis | 4 | |
| Acute bacterial endocarditis | 2 | |
| Appendicitis | 6 | |
| Meningitis | 1 | |
| Acute pancreatitis | | 1 |
| One case each of: acute sinusitis with sepsis, retropharyngeal abscess, cancrum oris, pyarthrosis with sepsis, decubitus ulcer with sepsis, tenosynovitis with sepsis, cellulitis with sepsis; peritonitis following: volvulus, perforated colonic ca., perforated bladder ca., perforated uterine ca., and perforated duodenal ulcer; acute cholecystitis, acute cholecystitis with sepsis, ca. gall bladder, subphrenic abscess. | | |
| Pyelonephritis | 7 | |
| Cystitis with sepsis | 1 | |
| Pyonephrosis with sepsis | 1 | |
| *Genito-urinary:* | | |
| Uremia | 3 | |
| Postop. nephrolithotomy | 1 | |
| Postop. cystolithotomy | 1 | |
| *Gastro-intestinal* | 7 | |
| Consisting of one case each of: colonic ca. with metastasis, postop. rectal ca., postop. colonic ca., strangulated femoral hernia, cirrhosis of liver, cirrhosis with hemorrhage, gastro-intestinal bleeding—cause? | | |
| *Infection:* | | |
| *Miscellaneous* | 9 | |
| Consisting of one case each of: postop. acoustic neuroma, leukemia, agranulocytosis, Hodgkin's, lymphosarcomatosis, hemochromatosis, pheochromocytoma, air embolism, unknown. | | |
| Unknown with coma | | 2 |
| *Cardiovascular:* | | |
| Acute coronary occlusion | 39 | 1 |
| Congestive cardiac failure | 23 | |
| Gangrene of foot with sepsis | 3 | 1 |
| Postop. amputation for gangrene | 18 | |
| Postop. amputation for gangrene and bronchopn. | 1 | |
| Postop. amputation for gangrene and coronary occlusion | 2 | |
| Cerebrovascular accident | 6 | |
| Pulmonary embolism | 2 | |
| *Pulmonary:* | | |
| Lobar pneumonia | 9 | |
| Bronchopneumonia | 5 | 2 |
| Lung abscess | 3 | 2 |
| Pulmonary edema | 1 | |
| Carcinoma bronchus and metastasis | 1 | |
| Pulmonary tuberculosis | 3 | |
| Disseminated tuberculosis | 1 | |
| Pyopneumothorax | 2 | |

TABLE 3.—NECROPSY FINDINGS IN 113 POSTMORTEM EXAMINATIONS.

| | |
|---|---|
| *Cardiovascular:* | |
| Arteriosclerosis | 78 |
| Coronary sclerosis | 64 |
| Acute coronary occlusion | 23 |
| Old coronary occlusion | 8 |
| Congestive heart failure | 16 |
| Rheumatic endocarditis | 15 |
| Hydrothorax | 13 |
| Enlarged heart | 8 |
| Bacterial endocarditis | 3 |
| Acute pericarditis | 2 |
| Cerebral thrombosis | 5 |
| Patent foramen ovale | 4 |
| Calcified aortic stenosis | 2 |
| Myocardial fibrosis | 11 |
| Miscellaneous | 7 |
| One case each of: calcified mitral valve, air embolism, saddle embolus of aorta, iliac vein thrombosis, portal vein thrombosis, hepatic vein thrombosis, femoral artery thrombosis. | |
| *Endocrine:* | |
| Thyroid adenoma | 8 |
| Colloid goiter | 3 |
| Hyperplastic thyroid | 1 |
| Atrophy of thyroid | 1 |
| Cortical adenoma of adrenal | 8 |
| Cortical hyperplasia of adrenal | 2 |
| Pheochromocytoma | 1 |
| Aplastic testis | 3 |
| *Liver:* | |
| Chronic passive congestion | 20 |
| Cirrhosis | 8 |
| Fatty infiltration | 15 |
| Hepatic artery thrombosis and infarction | 4 |
| Hepatic abscess | 1 |
| Hepatitis | 1 |
| Hemochromatosis | 1 |

TABLE 3.—NECROPSY FINDINGS IN 113 POSTMORTEM EXAMINATIONS. (*Continued.*)

*Gall Bladder:*
- Acute cholecystitis . . . . . 3
- Chronic cholecystitis . . . . . 17
- Choledocholithiasis . . . . . 3
- Cholesterol infiltration . . . . 2
- Cholelithiasis . . . . . 19
- Spontaneous choledochoduodenostomy . . . . . 1

*Chest:*
- Lobar pneumonia . . . . . 4
- Bronchopneumonia . . . . . 43
- Pulmonary edema . . . . . 29
- Pleurisy with effusion . . . . 2
- Pulmonary embolism . . . . . 12
- Bronchiectasis . . . . . 4
- Embolic abscesses . . . . . 1
- Bronchopleural fistula . . . . 1
- Mediastinitis . . . . . 2
- Bronchogenic carcinoma . . . . 1
- Lung abscess . . . . . 3
- Pyopneumothorax . . . . . 2
- Tuberculosis . . . . . 53
  (Primary, 17; disseminated, 7; caseous, 7; fibrotic, 9; cavitation, 3; calcified nodes, 9; exudative, 1.)

*Spleen and Blood:*
- Infarcts . . . . . 7
- Septic spleen . . . . . 13
- Miscellaneous . . . . . 7
  One case each of: thrombosis splenic vein, Hodgkin's, aleukemic mylosis, tuberculosis, calcified aneurysm splenic artery, atrophy, lymphosarcomatosis.

*Neurologic:*
- Brain tumor . . . . . 1
- Tabes dorsalis . . . . . 1

*Miscellaneous:*
- Fractured femur . . . . . 2
- Persistent thymus . . . . . 1

*Infections:*
- Sepsis . . . . . 17
- Acute otitis media . . . . . 2
- Lateral sinus thrombosis . . . 1
- Acute mastoiditis . . . . . 2
- Carbuncle . . . . . 3
- Cellulitis of foot . . . . . 2
- Gangrene with amputation . . 11
- Gangrene without amputation . 1
- Meningitis . . . . . 1
- Alveolar abscess . . . . . 1
- Cellulitis of abdominal wall . . 2
- Cellulitis of stump . . . . . 6
- Miscellaneous . . . . . 6
  One case each of: metastatic brain abscess, tenosynovitis (acute), subphrenic abscess, pyoarthrosis, brain abscess, cellulitis of neck.

*Gastro-intestinal:*
- Gastric ulcer . . . . . 5
- Acute gastritis . . . . . 4
- Erosions of stomach . . . . 3
- Gastric ca. . . . . 1
- Gastric myoma . . . . . 3
- Gastro-jejunal ulcer . . . . 1
- Duodenal ulcer . . . . . 6
- Duodenal ulcer perforated . . 1
- Intestinal obstruction . . . 3
- Ileojejunitis . . . . . 3
- Ulcerative colitis . . . . . 2
- Ca. of colon . . . . . 4
- Ca. of rectum . . . . . 1
- Colonic diverticulæ . . . . 4
- Colonic polyposis . . . . . 9
- Acute appendicitis . . . . . 5
- Peritonitis . . . . . 6
- Ascites . . . . . 4
- Meckel's diverticulum . . . . 2
- Miscellaneous . . . . . 5
  One case each of: cancrum oris, peptic ulcer esophagus, esophageal varices, duodenal erosions, chyloma of jejunum.

*Pancreas:*
- Lipomatosis . . . . . 26
- Fibrosis . . . . . 5
- Hyalinized islets . . . . . 2
- Chronic pancreatitis . . . . 1
- Subacute pancreatitis . . . . 1
- Pancreatic cyst . . . . . 1
- Fat necrosis . . . . . 2
- Atrophy . . . . . 7

*Genitalia:*
- Fibroids . . . . . 4
- Ovarian cyst . . . . . 1
- Tubo-ovarian abscess . . . . 3

*Bladder:*
- Cystitis . . . . . 13
- Diverticulum . . . . . 1
- Carcinoma . . . . . 1
- Calculus . . . . . 1

*Prostate:*
- Hypertrophy . . . . . 8
- Carcinoma . . . . . 1
- Thrombosis peri-prostatic plexus . 2

*Kidneys:*
- Nephrosclerosis . . . . . 12
  (Glomerulonephritis, 0)
- Pyelitis . . . . . 15
- Cortical abscess . . . . . 1
- Calculi . . . . . 3
- Renal vein thrombosis . . . . 1
- Infarctosis . . . . . 4
- Miscellaneous . . . . . 3
  One case each of: amyloid, Kimmelsteil, hypernephroma.

The degenerative diseases such as arteriosclerosis, gangrene, retinitis, coronary artery occlusion, and cataract, account for the largest percentage of admissions. This perhaps can be partially explained by the preponderance of the old age group in the hospital admissions; the group above 61 years alone comprising half the total admitted. This group also accounted in the main for the malignant neoplasms, terminal bronchopneumonias, sepsis, uremia, and cerebral accidents.

The well-known frequency of staphylococci infections of the skin is borne out by the large number recorded in this series. Yet, on the other hand, the incidence of erysipelas was low. The finding of tuberculosis was usually incidental, for it was most often inactive. Few active cases were observed since the rules of admission precluded their entry into the hospital's general wards. The singular frequency of mastoiditis due to the pneumococcus Type III is to be noted and a detailed report of this association is forthcoming.

The low incidence of admissions for upper respiratory infections and acute sinusitis is due to the fact that hospitalization was advised only in the presence of ketosis.

Lung abscess seemed to be more common in diabetic than in nondiabetic patients in this hospital.

The expected high incidence of gall bladder disease was observed in this group because of the preponderance of females in the middle age or elderly group. An unexpected finding was the number of patients with peptic ulcer, an incidence more than twice that reported by Joslin.

Hyperthyroidism with true diabetes mellitus comprised the largest group of associated endocrine diseases, a finding needing no discussion.

Two conditions not included in this study were arthritis and neuritis. The omission was purposeful in view of the variability of the diagnostic criteria.

Table 2 presents the compilation of the principal causes of death in this series of patients. Only the most important conditions which actually precipitated the death of the patient is reported in this table. The outstanding finding is the number of deaths attributed to cardio-vascular disturbances, the actual percentage being 48.6%. This can be correlated with the fact that 55.4% of patients admitted showed clinical evidence of cardio-vascular disease.

The next important group is the infections which accounted for 23.3% of the mortalities. This does not include pulmonary infections. If the latter be included, the figure rises to 37.3%. The high mortality is undoubtedly related to the fact that hospitalization is restricted to those infections which can no longer be treated on an ambulatory basis. These figures are "weighted" by the high mortality rate in lung abscess, lobar pneumonia, and sepsis. On the other hand, infections such as abscesses including carbuncles, which

are amenable to surgery, by virtue of the availability of insulin therapy, showed a much lower mortality, namely 8.6%.

In Table 3 are listed the autopsy findings in 113 patients. These are published merely to show the excellent agreement of our findings with those previously reported.

**Summary.** The data presented show that in spite of the availability of insulin therapy, the diabetic still presents the same complications as he has in the past.

## THE INCIDENCE OF TRICHINOSIS IN NEW YORK CITY.*

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The incidence of human infestation by *Trichinella spiralis* has received widespread publicity in recent years both in lay and scientific reading matter. The range in the figures reported varies from 3.5[4] to 36%[2] from various parts of the United States (Ann Arbor, Detroit, Cleveland, Louisiana), with a probable average incidence of about 17% throughout the country. This latter estimate is based on a comprehensive study of over 3000 human diaphragms obtained at necropsy from a widespread area of the country and reported by the National Institute of Health.[5] In several recent papers on the incidence of trichinosis all the previous incidence studies are summarized in tabular form.[1,3]

The present study was undertaken in order to discover the incidence of human infestation with *T. spiralis* in New York City by the use of a combination of digestion, press, and histologic methods on autopsy material, and to evaluate the relative efficacy of these methods to detect the presence of infestation.

**Material.** The muscles taken for study were removed from bodies selected at random daily from the large number of cases necropsied by the Office of the Chief Medical Examiner in the Borough of Manhattan. These necropsies were carried out on cases of homicidal, suicidal and accidental deaths, deaths from poisoning, drowning and other types of asphyxia, also sudden and unexpected deaths from natural causes. Only bodies of adults

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in a good state of preservation were utilized as a source of material. No attempt to select cases on the basis of age, sex, race, nationality, religion, economic status, or diagnosis was made. No known case of trichinosis was included in this series. The cases necropsied by the Office of the Chief Medical Examiner are a representative sample of the various racial strains and the economic levels of the population of New York City. A total of 100 cases was investigated: 83 males and 17 females; 79 were white, 29 black. The ages varied between 17 and 74 years, with 30 cases in the fourth decade, 25 in the fifth and 39 in the sixth decades.

Liberal samples of material (approximately 25 gm. from each site) were removed from each diaphragm, the intercostal, pectoral and psoas muscles, and placed in separate Petri dishes for study by the methods described below. Six samples were obtained from each case.

**Methods.** 1. *Examination by Press.* About 2 gm. of each muscle sample from each case were cut into small fragments and examined directly in a special press* through a binocular microscope (3.2 and 10x objectives, 10x oculars). Each specimen was examined systematically and if parasites were found the number of larvæ or cysts recorded. In addition, a piece of diaphragm, 2 by 2 cm. was stripped of its membranes and examined *in toto* in the press.

2. *Histologic Examination of Formalin Fixed Tissue.* Blocks of muscle from each of the samples used for digestion were fixed in 10% formalin and embedded in parlodion. Sections were cut 10 mu thick and approximately every tenth section was selected for staining with hematoxylin and eosin. Five to 10 sections were stained from each of 6 blocks in each case making a total of from 30 to 60 sections from the 6 muscle sites. The muscle fibers were sectioned longitudinally and a large area of muscle, approximately $\frac{7}{8}$ inch square, was available for histologic examination.

3. *Digestion.* A combined total of 50 gm. of muscle selected from 6 of the sites described, including the diaphragm in all cases, was used for digestion. The material was finely chopped or ground and placed in a 2 liter beaker containing 1000 cc. of digestion fluid (5 G pepsin, 7 cc. hydrochloric acid, Sp. gr. 1.19, 1000 cc. tap water). The mixture is incubated at 37° C. for 18 to 24 hours and stirred frequently. When removed from the incubator the beaker is allowed to stand for 15 to 20 minutes. The supernatant fluid is carefully drawn off by suction until the fluid level is $1\frac{1}{2}$ inches from the bottom, leaving about 450 cc. The remaining mixture is then filtered through a single layer of cheese cloth (mesh 20–22) into a 450 cc. cylinder, 2 inches in diameter and 12 inches in height. It is allowed to settle 30 to 45 minutes and the supernatant liquid drawn off by suction until the fluid level is 3 inches from the bottom leaving about 100 cc. in the cylinder. The latter is now mixed with warm water which is added until the cylinder is full. This washes the sediment and floats particles of fat, muscle, and connective tissue to the top. The mixture is allowed to stand 30 to 45 minutes and the supernatant liquid again carefully removed by suction until the fluid level is 3 inches from the bottom, leaving about 100 cc. in the cylinder. The remaining mixture is transferred to two 50 cc. conical centrifuge tubes and centrifuged at 1000 R.P.M. for 3 minutes. The supernatant fluid is again drawn off by hand using a bulb and pipette, leaving 2 cc. of suspended sediment at the bottom of each centrifuge tube. This entire suspension is then examined microscopically drop by drop on a

* Two brass plates, each $3\frac{3}{4}$ by $3\frac{3}{4}$ by $\frac{3}{16}$ inches, with the center cut out as a circle $2\frac{1}{4}$ inches in diameter, countersunk $\frac{7}{16}$ inches and recessed $\frac{1}{16}$ inch, are used as frames to hold together two plates of glass, each $2\frac{3}{4}$ inches in diameter and $\frac{3}{16}$ inch thick. Eight set screws $\frac{3}{16}$ inch diameter and $\frac{1}{2}$ inch long are fixed in one of the plates around the circular cut-out about $\frac{1}{4}$ inch from its edge. The other plate is appropriately drilled to permit the screws to pass through it freely. Both plates and glass are held and pressed together with wing nuts.

large slide (1½ by 3 inches) using a mechanical stage and binocular microscope (3.2 and 10x objectives and 10x oculars). If positive, the number of larvæ or cysts is recorded.

**Results.** In 100 cases studied, there were 22 that were positive for trichinæ by all methods combined, or an incidence of infestation by *T. spiralis* of 22% in this series of violent and sudden deaths in New York City. In the tables below (Tables 1 to 4), the results obtained in this study are presented and analyzed. Typical findings in a positive case are illustrated in Fig. 1 (*A* to *D*).

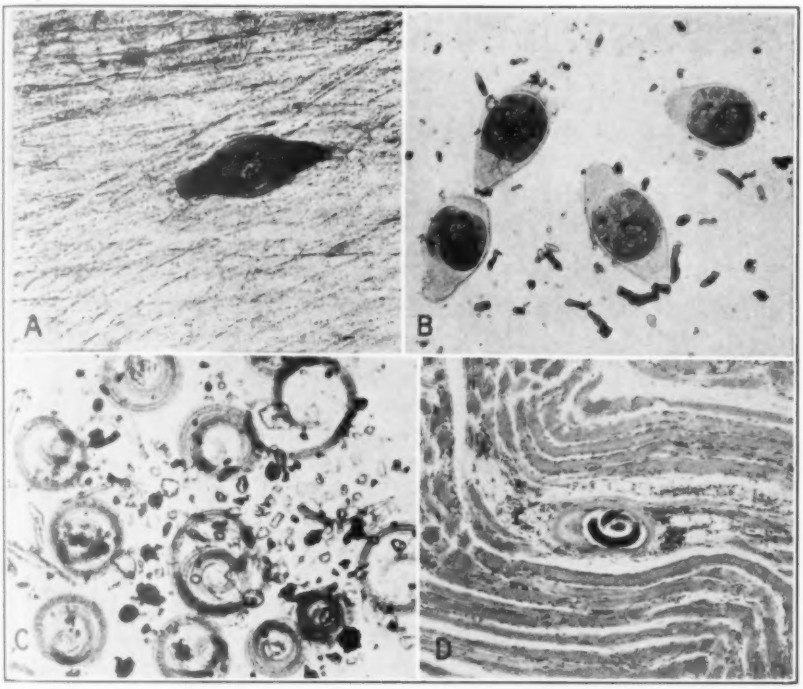


FIG. 1.—Findings in a positive case of infestation by *Trichinella spiralis*. *A*, Press preparation, encysted larva showing bipolar calcification, 16 mm. objective. *B*, Digestion, washed sediment. Encysted larvæ of *T. spiralis*, 16 mm. objective. *C*, Digestion, washed sediment. Completely freed young living larvæ of *T. spiralis*, 16 mm. objective. *D*, Histologic section. Encysted parasite. Focal myositis, 16 mm. objective. (Hematoxylin and eosin stain.)

**Comments.** *Press Method.* Eight cases of the entire series were positive for trichinæ by this method or an incidence of only 8% if this method alone had been employed. These 8 positive cases obtained by press represent 36.3% of the entire 22 positives in the series. All of the cases positive by press were also positive by digestion and in addition, 7 of them were positive by the histologic section method. Only 1 of the positive press cases was negative by his-

TABLE 1.—ANALYSIS OF POSITIVE CASES.

| Case No. | Press. | | | Digestion, larvæ per 50 gm. muscle. | Histologic examination. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pect. | Dia. | Psoas. | | Total sections. | Blocks, pos. | Slides, pos. | Total parasites. | Myositis. |
| 2 | 0 | 0 | 0 | 0 | 50 | 1 | 4 | 4 | + |
| 3 | 0 | 0 | 0 | 1 | 52 | 0 | 0 | 0 | + |
| 14 | 0 | 0 | 0 | 6 | 35 | 0 | 0 | 0 | + |
| 18 | 0 | 2 | 0 | 3 | 50 | 1 | 1 | 1 | + |
| 20 | 0 | 4 | 0 | 13 | 39 | 3 | 3 | 3 | − |
| 22 | 1 | 3 | 2 | 143 | 30 | 3 | 8 | 12 | + |
| 27 | 0 | 1 | 0 | 16 | 36 | 0 | 0 | 0 | + |
| 29 | 0 | 2 | 0 | 25 | 50 | 3 | 10 | 10 | + |
| 35 | 0 | 0 | 0 | 14 | 40 | 1 | 2 | 2 | + |
| 36 | 14 | 78 | 6 | 760 | 60 | 6 | 60 | 500 | + |
| 40 | 0 | 0 | 0 | 7 | 26 | 0 | 0 | 0 | − |
| 41 | 0 | 0 | 0 | 2 | 26 | 0 | 0 | 0 | − |
| 56 | 0 | 0 | 0 | 2 | 36 | 0 | 0 | 0 | + |
| 59 | 0 | 6 | 0 | 63 | 36 | 1 | 3 | 3 | + |
| 60 | 0 | 0 | 0 | 6 | 35 | 0 | 0 | 0 | + |
| 66 | 0 | 0 | 0 | 7 | 32 | 0 | 0 | 0 | − |
| 68 | 0 | 0 | 0 | 31 | 31 | 2 | 3 | 3 | + |
| 71 | 0 | 0 | 0 | 1 | 24 | 0 | 0 | 0 | − |
| 77 | 0 | 0 | 0 | 6 | 30 | 0 | 0 | 0 | − |
| 80 | 0 | 0 | 0 | 9 | 38 | 0 | 0 | 0 | + |
| 93 | 0 | 0 | 0 | 21 | 36 | 2 | 6 | 6 | + |
| 97 | 2 | 12 | 0 | 310 | 24 | 4 | 10 | 12 | + |

TABLE 2.—COMPARISON OF RESULTS BY VARIOUS METHODS, 100 CASES.

| Method. | No. positive. | Per cent. |
|---|---|---|
| Press | 8 | 8 |
| Digestion | 21 | 21 |
| Histologic section | 11 | 11 |
| All methods combined | 22 | 22 |

TABLE 3.—DEGREE OF INFESTATION (DIGESTION).

| Larvæ per 50 gm. | No. of cases. |
|---|---|
| 1– 10 | 11 |
| 11– 50 | 6 |
| 51–100 | 1 |
| 101 and above | 3 |

TABLE 4.—AGE, SEX, COLOR AND CAUSE OF DEATH IN 22 POSITIVE CASES OF TRICHINELLA INFESTATION.

| Case No. | Age. | Sex. | Color. | Cause of death. |
|---|---|---|---|---|
| 2 | 33 | F | W | Fractured skull |
| 3 | 65 | M | W | Fractured skull |
| 14 | 35 | M | W | Alcoholism |
| 18 | 50 | M | W | Heart disease |
| 20 | 46 | M | W | Bullet wound |
| 22 | 30 | M | B | Heart disease |
| 27 | 39 | M | W | Alcoholism |
| 29 | 64 | M | W | Heart disease |
| 35 | 42 | M | B | Fractured skull |
| 36 | 32 | F | B | Ruptured aneurysm |
| 40 | 37 | F | B | Alcoholism |
| 41 | 27 | F | B | Stab wound |
| 56 | 32 | F | B | Cerebral hemorrhage |
| 59 | 59 | M | W | Heart disease |
| 60 | 42 | M | W | Fractured skull |
| 66 | 36 | M | B | Nitric acid poisoning |
| 68 | 72 | M | W | Multiple injuries |
| 71 | 61 | M | W | Fractured skull |
| 77 | 42 | M | W | Alcoholism |
| 80 | 30 | M | B | Alcoholism |
| 93 | 31 | M | W | Cerebral hemorrhage |
| 97 | 38 | M | W | Heart disease |

tologic section. Five of the 8 press positives revealed larvæ only in the diaphragms, while in the 3 remaining cases, larvæ were found in the pectoral, psoas, and intercostal muscles as well as in the diaphragms. Apparently, the press method alone cannot be utilized in evaluating the degree of infestation, if one compares the results obtained by this method with those obtained by digestion. Since the press method would probably reveal only about one-third of the positive cases in any series studied, it cannot be relied on solely in any incidence study. Nevertheless, since press examination is a very simple procedure and since the muscle utilized can be submitted subsequently to digestion, it is suggested that this method be employed routinely in the preliminary examination of biopsy material for the diagnosis of trichinosis. It must be appreciated, however, that the press examination of the usual small specimen removed at biopsy from a single muscle may be negative for trichinæ, even though there is strong clinical evidence to support the diagnosis of trichinosis.

An interesting observation was noted during press examinations of several of the positive diaphragms. Occasionally, old, calcified, dead trichinæ cysts as well as young, viable larvæ, were found in the same specimen. This would indicate that reinfection in man does occur.

*Digestion.* Of the 22 positive cases in the entire series 21 were positive by digestion. Thus digestion alone would have detected 95.4% of all the positives in the series and would have yielded an incidence of 21% for the whole study or only 1% less than the final incidence obtained as a result of all the methods combined.

Ten of the 22 positive cases were detected by digestion alone and not by the 2 other methods employed. It is noteworthy that in the cases detected by digestion alone there were less than 10 larvæ per gram of muscle. Apparently digestion is of great value in discovering light infections, though, to be sure, the percentage of positives would be much less if smaller amounts of tissue were taken for digestion. Without digestion, the incidence in this series would have been only 12%. The digestion method detected 13 more positive cases than did the press method and 10 more than were found by the histologic method.

It seems desirable therefore to include digestion studies in any survey which aims to detect the highest possible incidence of trichinosis in postmortem material. The digestion technique can be safely employed alone utilizing moderate amounts of diaphragm with reasonable certainty that a fairly true estimate of the incidence of trichinosis would be revealed in a postmortem survey.

From the standpoint of laboratory diagnosis of trichinosis on biopsy material, digestion should be carried out even though other methods are unsuccessful. It has been our experience in many cases to find larvæ by digestion when press and histologic examinations

were negative. Digestion of the small amount of muscle usually obtained by biopsy is a very simple procedure and can be carried out in any laboratory. The muscle tissue obtained at biopsy may be treated in the following manner: A very small sample of the biopsy is placed in formalin for histologic study which may reveal a suggestive myositis even though the parasites are not found. The remainder of the specimen is then examined by press and if this examination is negative, by digestion. If one is interested in correlating the clinical severity of the disease with the number of larvæ in each gram of muscle, the specimen is weighed and submitted to digestion, so that the total number of larvæ or cysts in it can be counted.

In the present series only 1 of the positive cases was negative by digestion. In this case only 1 parasite was found in the diaphragm in 1 out of a total of 50 histologic sections prepared from 6 blocks of tissue.

In several cases showing the severest degree of infestation, attempts to demonstrate larvæ in the heart muscle were unsuccessful.

*Histologic Method.* Approximately 4000 histologic sections were examined in this study and in 11 cases parasites were detected. Thus only half of the final total of 22% would have been obtained had this method alone been used. It is noteworthy that of the 600 blocks from which 4000 sections were cut in the entire series, only 4.5% of the blocks and 2.7% of the sections were found to contain parasites. Of the 22 cases positive by all methods, only 20% of the blocks and 13.4% of the slides were positive and of the 11 positive cases discovered histologically, 40% of the blocks and only 25% of the sections cut from them were found to contain parasites.

Histologic examination did detect 4 positive cases which were negative by press including 1 which was also negative by digestion. The case detected histologically and not by digestion would have changed the final total incidence of infestation by only 1% if it had not been discovered. Inspection of Table 1 reveals a serious drawback in the value of the histologic method in that it fails in most cases to detect infections which yield less than 10 larvæ per 50 gm. of muscle by digestion.

Interstitial focal myositis was noted in most of the positive cases. In some sections in which parasites were not found the myositis was so intense as to suggest that if more or the next sections had been examined, parasites would have been found. Myositis was also observed in some cases which were negative by all the methods and it was absent in several of the milder infections.

The histologic examinations carried out in this study were time consuming and laborious. Only half the positive cases in this series were confirmed by this method and in these positive cases parasites were found in relatively few sections out of the large number exam-

ined. The histologic method used alone in any survey is therefore unreliable and impractical. The rare positive case which might be discovered by histologic examination and missed by press or digestion, hardly justifies the inclusion of this method with the other methods in any postmortem incidence study.

In the laboratory diagnosis of trichinosis on biopsy material it must be emphasized again that unless the infection is very heavy and widespread, the likelihood of finding parasites in a few slides from a random block of a single muscle is small. Often in a clear-cut clinical case of trichinosis the histologic examination of the biopsied muscle fails to reveal any parasites, although it may reveal a suggestive myositis.

**Summary and Conclusions.** 1. In a series of 100 bodies of persons dying by violence or suddenly from natural causes in New York City, studied by a combination of press, digestion and histologic methods, there were 22 cases of infestation by *T. spiralis*, an incidence of 22%. This would suggest that the occurrence of human trichinosis in New York City is considerable and well beyond clinical appreciation and recognition of the disease.

2. Digestion of large amounts of muscle, preferably the diaphragm, is the most feasible and reliable method to determine the incidence of infestation in man and will detect the largest number of positive cases in contrast to other methods, especially if the infestation is light.

3. The relative efficacy in detecting positive cases of infestation in this series by the methods of digestion, histologic examination and press was in the ratio of 21 to 11 to 8, respectively. Without the use of the digestion method the incidence determined in this series would have been 12%.

4. In addition to routine histologic examination, muscle obtained by biopsy for diagnosis should be studied routinely by press and then submitted to digestion to determine the number of larvæ per gram of muscle. The procedures are simple and can be performed in any laboratory. They will reveal more positive cases of infestation than the method of histologic examination used alone. Random histologic sections from a single small block of biopsied muscle will frequently be negative despite strong clinical and laboratory evidence of trichinosis.

5. Reinfection in man by *T. spiralis* does occur.

We wish to acknowledge with thanks the technical assistance of Ethyl Greenwald Ringer, A.B., and Morris Kolin, B.S.

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# NEGATIVE THERAPEUTIC AND METABOLIC EFFECTS OF SYNTHETIC ALPHA-TOCOPHEROL (VITAMIN E) IN MUSCULAR DYSTROPHY.

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In 1922 Evans and Bishop,[4] and later others, reported on the existence of a dietary constituent which was essential for normal reproduction in the rat. This substance was subsequently known as vitamin E. In later work Evans, his coworkers and others found that suckling rats born of mothers which had received a diet low in vitamin E developed paralysis of the skeletal musculature and a large number soon died. This occurred in spite of the fact that the mothers produced adequate amounts of milk for normal growth. The pathology of this experimental form of muscular paralysis has been reported to be associated with lesions of the nervous system by some investigators[3,12] but this has been denied by others.[2,7,8,15,16] These paralyses could be prevented by the administration of substances rich in vitamin E as late as the 15th day of life.

Subsequent investigators[6,8,13] were able to show that alpha-tocopherol was effective in curing or preventing the development of this experimental form of nutritional muscular dystrophy and more recently Knowlton, Hines and Brinkhous[11] reported that synthetic alpha-tocopherol acetate was efficacious in the cure and prevention of the experimental muscular dystrophy produced by vitamin E deficiency.

Owing to the reports of Bicknell[1] and of Stone[17] on the efficacy of vitamin E in the form of wheat germ oil or dried wheat germ in the treatment of some cases of muscular dystrophy and of atrophy, this study regarding the therapeutic and metabolic effect of synthetic *dl*-alpha-tocopherol acetate* in muscular dystrophy was undertaken. Such study was especially indicated because of the possibility, as some of the investigators[8,14] had pointed out, that other essential factors besides vitamin E might be present in the crude wheat germ oil extract which might be responsible for the therapeutic effect.

**Procedure.** A group of 5 cases of progressive muscular dystrophy, 4 male and 1 female, was chosen for this study, which was made entirely in 1940. These cases had been under our observation for from 2 to 7 years and the general clinical course of the condition was well known in each case. It will be noted from the protocols that 2 of the male patients (Cases 1 and 3) had older brothers who

* Synthetic *dl*-alpha-tocopherol acetate was used throughout this study; it was kindly supplied, in part, by Hoffmann La-Roche, Inc.

also had progressive muscular dystrophy. The female patient (Case 4) was of especial interest because her muscular weakness became manifest for the first time during a pregnancy.

The patients were placed on meat-free, low-purine diets for several days prior to treatment and total 24-hour specimens of urine were collected daily during this fore period. The patients were then permitted to eat a regular mixed diet and *dl*-alpha-tocopherol acetate was administered orally in increasing doses of from 9 mg. to 200 mg. daily for varying periods of from approximately 3 to 6 months as indicated in the protocols. At intervals of 1 to 2 weeks during the course of treatment and after treatment the patients were put on a meat-free diet for 2 consecutive days and total 24-hour specimens of urine were collected on these days. The creatinine and creatine in each 24-hour specimen of urine was determined quantitatively. The Folin method was used as adapted by Kassell[10] for the Pulfrich photometer.

**Clinical Histories.** Case 1. J. B., a male, age 9 years, was seen for the first time in 1938, at the age of 7, because of peculiar gait and some difficulty in climbing stairs. His brother also had suffered from progressive pseudohypertrophic muscular dystrophy and had been seen by us since 1933; he died in 1940 at the age of 15 years at which time he was totally incapacitated. The patient in 1933 was 18 months old and was reported to be walking, and apparently well. The rest of the family history as regards grandparents, maternal and paternal aunts and uncles and a sister was negative as to relevant illness.

*Physical Examination.* On March 9, 1940, before treatment, the patient showed involvement of upper and lower extremities. He walked with a shuffling and waddling gait and marked lordosis. He could not climb stairs. The power for flexion and extension at the elbow joints was weak; flexion of thighs on hips was very weak. There was some bilateral weakness of the quadriceps femoris muscles; dorsiflexion of both feet was limited in extent; plantar flexion was very strong and the calf muscles appeared hypertrophied. There were no fibrillary twitchings of the skeletal musculature; no sensory disturbances. The knee jerks, biceps and triceps reflexes were absent. The ankle jerks were active. The genitalia were somewhat hypoplastic, the testes being small and soft. The rest of the physical examination was negative.

*Alpha-tocopherol Treatment.* March 21 to April 6—3 mg. t.i.d. = 9 mg. daily.

April 6 to May 26—6 mg. t.i.d. = 18 mg. daily.

May 26 to May 31—9 mg. 4.i.d. = 36 mg. daily.

June 1 to Sept. 26—20 mg., 10 mg., and 20 mg. = 50 mg. daily.

Oct. 5 to Oct. 26—50 mg. 4.i.d. = 200 mg. daily.

*Course.* Since April 5, the family was of the opinion that the patient had more power in his upper extremities. They stated he could lift some heavy toys which he did not do before. Physical examination, however, failed to reveal any notable changes. The patient is still under observation (March, 1941) with condition essentially unchanged.

The metabolic changes are seen in Table 1.

Case 2.—M. Y., male, aged 14, had been under our observation because of difficulty in walking since 1933 when he was 3 years, 8 months old. His birth was normal. He was a bottle fed infant and did not present any feeding problem except between $2\frac{1}{2}$ and $3\frac{1}{2}$ years of age, at which time he had

frequent attacks of vomiting. He started to walk at 19 months of age. The family history was negative for any relevant illness. The patient was an only child of a second marriage. His father had had 3 children, 1 boy and 2 girls by the first wife. These children were all well. The patient had grown progressively worse during the past 7 years with involvement of both upper and lower extremities.

*Physical Examination.* The patient was still ambulatory at the time of the examination just prior to treatment with alpha-tocopherol. There was marked weakness in abduction of arms and in flexion and extension of forearms. The grip of both hands was weak but there was no atrophy of the interosseous muscles. The lower extremities showed marked weakness in flexion of thighs on hips and in extension of the legs. Dorsiflexion of feet was weak while plantar flexion was very good. There was marked lordosis of the lumbar spine. The knee jerks, biceps and triceps, tendon reflexes could not be elicited. The ankle jerks were present. The patient rose from the sitting position with great difficulty. Genitals appeared hypoplastic and pubic hair was just making its appearance.

*Alpha-tocopherol Treatment.* April 13 to June 1—6 mg. t.i.d. = 18 mg. daily.

June 1 to Sept. 7—20 mg., 10 mg. and 20 mg. = 50 mg. daily.

Sept. 14 to Sept. 28—20 mg., 10 mg. and 20 mg. = 50 mg. daily.

Sept. 28 to Oct. 10—No treatment.

Oct. 10 to Nov. 2—50 mg. alpha-tocopherol, 4.i.d. = 200 mg. daily.

*Course.* The parents of the child were of the opinion that his upper extremities were somewhat stronger as a result of the treatment. The physical examinations, however, failed to reveal any notable change. The patient is still under observation (March, 1941) with condition essentially unchanged.

CASE 3. M. T., male, aged 19, was first seen by us in 1933 at the age of 12. At that time the chief complaint was difficulty in walking up the stairs. His birth was normal. He was breast fed and as a baby had frequent colds. He began to walk at 13 months and appeared well up to 4 years when he began to have difficulty in walking up the stairs. His condition grew progressively worse and at present, although he is still ambulatory, he has involvement of both upper and lower extremities.

The family history was of interest in that there are 3 sisters who are well and 2 older brothers, 1 of whom, the oldest, was totally incapacitated by muscular dystrophy. The rest of the family history was negative for relevant illness.

*Physical Examination.* Patient had a marked lordosis and a waddling gait. He rose from the sitting position with great difficulty. The ability to abduct the arms was fairly good. Flexion and extension at the forearms was very weak. The grip in the hands was good. There was some weakness in the power to flex thighs, the hips, and considerable weakness in extension of the legs and dorsiflexion of the feet. Plantar flexion of the feet was very good. The calves of the legs appeared hypertrophic. The knee jerks, biceps and triceps, tendon reflexes could not be elicited. The ankle jerks were active. There were no fibrillary twitchings of the muscles and no sensory disturbances. The external genitals appeared hypoplastic.

*Alpha-tocopherol Treatment.*—July 6 to Sept. 12—20 mg., 10 mg., 20 mg. = 50 mg. daily.

Sept. 12 to Oct. 3—30 mg., 20 mg., 30 mg., 20 mg. = 100 mg. daily.

*Course.* Patient showed neither subjective nor objective improvement. He is still under observation (March, 1941) with condition essentially unchanged.

CASE 4.—E. S., male, aged 16, came under our care in 1933 at the age of 10 because of difficulty in walking. Examination at that time showed appreci-

able involvement of both upper and lower extremities. His birth was normal and he was bottle fed and presented no feeding problems. He had chicken-pox, whooping cough and acute otitis media during infancy and childhood. The family history was negative for relevant illness. There were no male siblings and only 1 other sister who was well.

*Physical Examination.* Patient was practically totally incapacitated presenting a picture of far advanced progressive muscular dystrophy.

*Alpha-tocopherol Treatment.* April 11 to June 5—6 mg. t.i.d. = 18 mg. daily.

June 5 to Sept. 30—20 mg., 10 mg., 20 mg. = 50 mg. daily.

Oct. 8 to Nov. 2—50 mg. 4 i.d. = 200 mg. daily.

*Course.* No notable change occurred as a result of the treatment. The patient is still under observation (March, 1941) with condition essentially unchanged.

CASE 5.—P. B., female, aged 43, married, came to our clinic in 1938 at the age of 41 because of weakness in upper extremities and difficulty in walking. She stated that in 1932, when she was in the second month of pregnancy, she noted that she was developing weakness in her upper extremities and difficulty in climbing stairs and had noted no physical difficulties before that time. However, she went through pregnancy and gave birth to a normal, healthy, female infant, who is now 8 years' old and in excellent health. The patient also noted that she was clumsy in handling the infant. Her condition grew progressively worse although she was still ambulatory at the time of the present investigation. The menstrual period had been normal and there was no history of miscarriages except that of a therapeutic abortion in the second month of pregnancy, subsequent to her first pregnancy. This was done because she felt that the pregnancy was increasing the weakness of her muscles. The family history was negative for any relevant illness.

*Physical Examination.* Patient had a waddling gait and marked lordosis of the back. She rose from the sitting position with difficulty. Power to abduct the arms was fairly good. There was marked weakness in flexion and extension of the forearms. The grip in both hands was very good. There was appreciable weakness in flexion and extension of the thighs on hips. However, the power for flexion and extension of the legs at the knees and for dorsiflexion and plantar flexion of the feet was very good. (NOTE: The marked weakness usually found in the quadriceps femoris and the tibialis anticus muscles, and previously noted in the 4 male patients, was absent in this case.) There were no sensory disturbances. The knee jerks and ankle jerks were present. The biceps and triceps tendon reflexes could not be elicited.

*Alpha-tocopherol Treatment.* March 18 to April 14—3 mg. daily.

April 14 to June 6—6 mg. t.i.d. = 18 mg. daily.

June 6 to July 15—20 mg., 10 mg., 20 mg. = 50 mg. daily.

July 15 to Aug. 1—Off treatment (thought she felt better while on treatment).

Aug. 1 to Sept. 12—50 mg. daily.

Sept. 12 to Oct. 28—50 mg. 4.i.d. = 200 mg. daily.

*Course.* As indicated above, the patient thought she was feeling better along toward the middle of her course of treatment. She said she thought she could do things with less stress although she did not think she had any increase in muscular power. Subsequently, however, she felt she was in no better condition and decided to discontinue her treatment completely. On physical examination there appeared to be some slight increase in power in flexion of thighs on hips and also the triceps reflexes could be elicited. She is still under observation (March, 1941) with condition essentially unchanged.

**Metabolic Observations.** It will be seen from the table that all of the cases had an appreciable creatinuria with rather low preformed creatinine excretions. The patient (Case 4) who was most disabled had the lowest preformed creatinine excretion per day. The preformed creatinine amounted to less than one-third of the "total creatinine"* excretion per day. Only 2 of the cases showed a tendency to a rise, the other cases showed practically no changes or a slight fall in creatinine excretion. The relative creatinuria continued to be marked throughout the period of study.

TABLE 1.—THE EFFECT OF THE ADMINISTRATION OF *dl*-ALPHA-TOCOPHEROL ACETATE (SYNTHETIC) ON CREATININE AND CREATINE EXCRETION IN CASES OF PROGRESSIVE MUSCULAR DYSTROPHY.

| Case No. | Period of treatment. | Daily dose (mg.). | Average urinary excretion per day. Preformed creatinine (gm.). | Total creatinine (gm.). | Creatine (gm.). |
|---|---|---|---|---|---|
| 1 | Before treatment | None | 0.22 | 0.62 | 0.48 |
| | Mar. 21–June 1 | 9–36 | 0.23 | 0.62 | 0.45 |
| | June 1–Aug. 27 | 50 | 0.21 | 0.60 | 0.44 |
| | Oct. 5–Oct. 26 | 200 | 0.20 | 0.62 | 0.47 |
| | Oct. 27–Dec. 14 | None | 0.23 | 0.68 | 0.54 |
| 2 | Before treatment | None | 0.24 | 0.51 | 0.38 |
| | April 13–June 1 | 18 | 0.25 | 0.64 | 0.45 |
| | June 1–Sept. 7 | 50 | 0.28 | 0.71 | 0.50 |
| | Sept. 14–Sept. 28 | | | | |
| | Oct. 10–Nov. 2 | 200 | 0.29 | 0.66 | 0.43 |
| | Nov. 2–Dec. 14 | None | 0.31 | 0.72 | 0.48 |
| 3 | Before treatment | None | 0.36 | 0.76 | 0.46 |
| | July 6–Sept. 12 | 50 | 0.33 | 0.65 | 0.38 |
| | Sept. 12–Oct. 4 | 100 | 0.30 | 0.61 | 0.36 |
| | Oct. 4–Nov. 30 | None | 0.28 | 0.54 | 0.30 |
| 4 | Before treatment | None | 0.16 | 0.51 | 0.41 |
| | Apr. 11–June 5 | 18 | 0.16 | 0.52 | 0.42 |
| | June 5–Sept. 30 | 50 | 0.16 | 0.51 | 0.41 |
| | Oct. 8–Nov. 2 | 200 | 0.14 | 0.48 | 0.39 |
| 5 | Before treatment | None | 0.58 | 1.04 | 0.52 |
| | Mar. 18–June 6 | 3–18 | 0.58 | 1.07 | 0.54 |
| | June 6–July 15 | 50 | 0.58 | 1.13 | 0.65 |
| | Aug. 1–Sept. 12 | | | | |
| | Sept. 12–Oct. 28 | 200 | 0.63 | 1.10 | 0.56 |
| | Oct. 28–Nov. 15 | None | 0.58 | 0.99 | 0.46 |

**Discussion.** It might be expected that any marked improvement in the skeletal musculature of the patients would be associated with a rise in the daily creatinine excretion associated with a decreased tendency to creatinuria. Furthermore, as was reported in a previous publication,[9] the proteins and the amino acids in the diet may readily affect the level of the abnormal creatine excretion without affecting the creatinine excretion, and this stability of the abnor-

* Total creatinine represents the sum of the preformed creatinine plus the creatine, which is determined as creatinine.

mally low creatinine excretion should render it a better guide to significant changes in the skeletal muscles, although alleviation of creatinuria is also important. It was also pointed out in the aforementioned report that as the muscular dystrophy progressed the creatinine decreased.[9] These clinical findings regarding creatinine and creatine metabolism differ from those reported by MacKenzie and McCollum[13] for experimental nutritional muscular dystrophy in animals. These investigators found that as the animals developed muscular dystrophy they also developed a marked creatinuria; however, the creatinine excretion remained practically unaltered. The first sign of therapeutic response in their animals was a drop in creatine excretion without any notable change in creatinine. It is possible that this difference in creatinine metabolism between our patients and the experimental animals may point to some fundamental difference in pathogenesis.

As was indicated previously, only 2 of the cases showed a rise in creatinine excretion. However, in spite of this small rise, the creatinine excretion continued to be abnormally low. The continued low creatinine output and marked creatinuria in all the cases was in keeping with the lack of any marked change in the physical condition of the patients. The slight improvement described by the patients is indicated in the protocols.

The results obtained with *dl*-alpha-tocopherol acetate as compared with those obtained by Bicknell and by Stone in their cases treated with wheat germ oil or dried wheat germ and vitamin B complex, raise several questions, whether the wheat germ preparations which they used contained other essential substances besides vitamin E, whether the added vitamin B complex played any rôle, or whether the types of muscular dystrophy which they treated were different from ours. No metabolic data are given by these investigators which could be used for comparison.

It is hoped that further study of the same clinical material using a therapeutic regimen similar to that of the above investigators may help to elucidate this problem.

**Summary and Conclusions.** 1. The metabolic and therapeutic effects of synthetic *dl*-alpha-tocopherol acetate in 5 cases (4 male and 1 female) of progressive muscular dystrophy are reported.

2. Two of the male patients had a familial history of the disease.

3. The marked therapeutic effects of wheat germ oil reported by some investigators were not obtained with the use of synthetic vitamin E.

4. Some differences in creatinine metabolism between experimental nutritional muscular dystrophy in animals and muscular dystrophy in man are pointed out.

5. The significance of the findings are discussed and plans for further investigations are indicated.

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## ADDISON'S DISEASE: TREATMENT AND PROGNOSIS.

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During the past 7 years as various biochemical and physiologic discoveries were made, treatment for Addison's disease has been modified periodically. At the Mayo Clinic, for example, from 1933 to 1935 patients were treated with liberal amounts (10 gm.) of sodium chloride and injections of cortical extract that were prepared by Kendall. During the latter part of this period sodium citrate (5.0 gm.) was administered in conjunction with the sodium chloride. Cortical extract was used during crises and regularly at other times by those patients (the majority) who could not get along without it.

In 1935 a diet that was low in potassium was added as an adjunct to the therapeutic measures previously employed.[9] After this change had been made it was found that some patients required the use of cortical extract every day; some, only during periods of stress; and others, not at all. It was our clinical impression that patients sustained on this regimen needed less cortical extract, had fewer crises and were more able to carry on normal activities than those whose diet was unrestricted. The low potassium diet, however, required careful preparation and was limited in variety of foods.

In 1939, desoxycorticosterone acetate was made available for clinical use. A series of steroid compounds were isolated almost simultaneously from the adrenal cortex by Kendall and his associates[1,2,3] and by Reichstein;[4] shortly thereafter Steiger and Reichstein[6] synthesized desoxycorticosterone acetate. The powerful effects of this compound on the excretion of sodium, potassium, chloride and urea were appreciated promptly by Thorn,[7] who first

applied it clinically in the treatment of Addison's disease. Subsequently it was used at the Mayo Clinic and elsewhere.

In the evaluation of the results obtained in the treatment of Addison's disease it is important to bear in mind that prior to the advent of modern substitutional therapy the prognosis was exceedingly grave. Although in very exceptional instances untreated patients and patients treated by measures that would now be regarded as ineffectual lived for as long as 10 years after the onset of symptoms, comparatively few were alive 5 years after the onset of symptoms. It is equally important to remember that treatment for chronic adrenal insufficiency does not cure or arrest tuberculosis and that, even if perfect replacement therapy were available, early death from tuberculosis would occur in an appreciable number of instances. Finally, the prognosis in individual cases of Addison's disease in which the etiologic factor is tuberculosis is unquestionably influenced by the amount of adrenal tissue that has not been destroyed by the tuberculous process. There is no available method at the present time by which the amount of this remnant of healthy cortical tissue can be determined. To make matters more complicated, there is reason to believe that in recent years there have occurred a decrease in the incidence of tuberculosis and an increase in incidence of atrophy as the cause of Addison's disease. If such is the case, the influence on prognosis can only be conjectured. It is evident, therefore, that a mere statistical analysis of survival is unlikely to give a picture that is free from distortion.

In 1938, Rynearson, Snell and Hausner[5] presented data on 43 cases of Addison's disease in which the patients were examined at the Mayo Clinic between October, 1933, and July, 1937. We wish to present data on 67 additional cases in which the patients were seen between July 1, 1937, and December 31, 1940, inclusive, together with an analysis of therapeutic results that were obtained in both groups.

Of these 110 cases there was evidence of tuberculosis (either active or arrested) involving the lungs, bones, kidneys, genitals or cervical lymph nodes in 37 (34%). It is probably safe to assume that atrophy was the etiologic factor in the majority of the remaining 73 cases. Among the entire group of 110 cases, associated disease that might have influenced mortality* and degree of morbidity was present in 41 cases. These associated diseases included calcareous aortic stenosis, latent syphilis, duodenal ulcer, unexplained fevers, rheumatic endocarditis, migraine, hypertension,† renal calculi and agitated depression.

* A curiously high incidence of disorders of the thyroid was encountered in addition to the usual cases of low basal metabolic rate. Four patients had had thyroidectomy performed several years prior to the onset of Addison's disease because of toxic goiter. Three additional patients were found to have adenomatous goiters without hyperthyroidism and 2, diffuse colloid goiters.

† This case is of interest because of the fact that hypertension persisted in spite of Addison's disease, even though the patient was not treated with desoxycorticosterone acetate. At necropsy, the adrenal glands were found to be atrophic.

Fortunately for the purpose of this study there were 19 patients* who refused to adhere to the low potassium diet after they left the hospital. These patients, however, did continue to take sodium chloride, sodium citrate and varying amounts of cortical extract. They, therefore, comprise a fairly satisfactory control group which one may compare with the group of patients who did adhere to the low potassium diet.

Table 1 shows the difference between the control group and the group treated with the low potassium diet. Among the latter, 88% lived more than 1 year and 40% lived more than 4 years after beginning treatment. Of the control group, only 53% lived more than 1 year, and only 18% were alive at the end of 4 years. The difference in survival is even more striking if it is calculated from the date of onset of symptoms; however, this method of calculation is open to the objection that the exact time of onset of symptoms usually cannot be determined.

TABLE 1.—SURVIVAL RATES: COMPARISON OF PATIENTS RECEIVING LOW POTASSIUM DIET WITH A CONTROL.†

| Period years. | Low potassium diet. | | | Control group. | | |
|---|---|---|---|---|---|---|
| | Patients traced.‡ | Lived beyond indicated period. | | Patients traced.‡ | Lived beyond indicated period. | |
| | | No. | Per cent. | | No. | Per cent. |
| 1 | 50 | 44 | 88 | 19 | 10 | 53 |
| 2 | 34 | 23 | 68 | 18 | 4 | 22 |
| 3 | 25 | 16 | 64 | 13 | 3 | 23 |
| 4 | 10 | 4 | 40 | 11 | 2 | 18 |

The mean length of life of those who died after the diagnosis had been made at the clinic was 2 years in the group which was treated with the low potassium diet; of those whose diet was not restricted, 1 year. Calculated from the onset of symptoms the mean duration of the disease among those who died in the former group was 3.6 years and in the latter, 2.2 years.

Of the 23 patients who died while being treated with the low potassium diet, 11 died in crisis. In the remaining 12 cases, death occurred because of an associated complication which in some instances probably would not have proved fatal if the patient had not also had Addison's disease. Among these complications were acute appendicitis, quinsy, unexplained fever and active tuberculosis. One patient died after flagrantly neglecting his diet.

* Eight additional patients were excluded from the control group because of severe complicating disease such as advanced tuberculosis.

† The controls followed the same treatment as the patients on low potassium diets except for restriction of the intake of potassium. This treatment included an adequate supply of sodium chloride and sodium bicarbonate together with daily or periodic injections of adrenocortical extract.

‡ Inquiry as of July 1, 1940. The 1-year group comprises patients seen at the Clinic whose condition was diagnosed as Addison's disease 1 or more years prior to the time of inquiry, that is, patients seen June 30, 1939, or earlier; the 2-year group comprises patients seen as of June 30, 1938, or earlier, and so forth.

A woman, after adhering rigidly to her diet for several months, died dramatically within 6 hours after a dietary debauch. Two patients discontinued the diet and were treated with desoxycorticosterone acetate elsewhere. One of these was treated by the subcutaneous implantation of a very large amount of desoxycorticosterone acetate. At necropsy a few days later hydrothorax, ascites, hydropericardium and edema were present. In the other, hypertension occurred before death.

We know of 18 patients who are still being sustained by the low potassium diet, sodium chloride and sodium citrate. Only 3 of these patients require cortical extract regularly; the remainder use it during periods of stress such as respiratory infections and other intercurrent illnesses. Of these 18 patients, 8 are able to work at their regular occupations the entire year, 2 are able to work except during very hot weather, 7 are working part time, and 1 is unable to work at all.

Fourteen patients who had been maintained on the low potassium diet were treated subsequently with daily hypodermic injections of desoxycorticosterone acetate. At the same time the low potassium diet was discontinued. Following the change in treatment the health of these patients improved so that at present all but 2 of them are able to carry on normal activities.

Nine patients were treated with a *low potassium diet, high intake of sodium salts, and desoxycorticosterone acetate.* This method of therapy did not produce good results. Only 1 patient remained well. Two others contracted diarrhea and other symptoms which were interpreted by them as suggestive of impending crisis. These symptoms disappeared in 1 after discontinuance of the desoxycorticosterone acetate and in the other after discontinuance of the low potassium diet.

Five of the 6 other patients treated with desoxycorticosterone acetate while receiving a low potassium diet died within 2 months after beginning this type of treatment. Another died 6 months after treatment was instituted. All of these deaths, it is important to emphasize, occurred during the summer of 1939 when the danger of the concurrent use of a low potassium diet, a high sodium intake and desoxycorticosterone acetate was still unknown.

The terminal illnesses of these 6 patients are of considerable importance, as they illustrate not only the dangers of a high sodium, low potassium intake when used in conjunction with desoxycorticosterone acetate but also the dangers of this substance itself and its limitations as complete replacement therapy.

**Case Reports.** One of the patients, a woman aged 39, became edematous while taking a low potassium diet, 10 gm. of sodium chloride, 5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. With the onset of edema the intake of sodium chloride was reduced to 6 gm. daily and the low potassium diet was discontinued. Nevertheless the edema persisted and the

blood pressure increased to 160 mm. of mercury systolic and 110 diastolic. Pulmonary edema and dilatation of the heart followed. Death occurred suddenly.

The blood pressure of another patient, a man, rose to 160 mm. of mercury systolic and 100 diastolic while he was taking only 2.5 mg. of desoxycorticosterone acetate and 6 gm. of sodium chloride daily. General malaise and tightness of the chest were terminal complaints. Death occurred at home. There is no information regarding edema.

The third patient, a woman, died at home 2 months after the onset of treatment. She was taking 10 gm. of sodium chloride, 5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. Her attending physician reported that cyanosis, coma, convulsions and hypertension (160/?) were terminal symptoms.

The fourth patient, a woman, felt well for some time after implantation of 368 mg. of desoxycorticosterone acetate. She took in addition 6 gm. of sodium chloride. The diet contained only 3 gm. of potassium. After the onset of tonsillitis death occurred within 3 days. There was not any terminal edema or hypertension.

The fifth patient was an emaciated woman who had been getting along on a low potassium diet. She was admitted to the hospital because of nausea, weakness and symptoms of crisis. These symptoms may have been precipitated by the very hot, humid weather which prevailed at that time. Treatment consisted of intravenous injections of sodium chloride and sodium citrate, 40 to 80 cc. of cortical extract and 10 mg. of desoxycorticosterone acetate daily. Death occurred 3 days after the onset of treatment. Hyperpyrexia and hypotension were terminal symptoms. At necropsy the significant findings were bilateral adrenal atrophy, hydrothorax and cardiac dilatation.

The therapeutic program in the sixth case consisted of a low potassium diet, 5 gm. of sodium chloride, 2.5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. Six months after the onset of this regimen the patient, a woman, suddenly died during sleep. There were no premonitory symptoms.

It became apparent from these unfortunate experiences that either we were not using desoxycorticosterone acetate to the best advantage or that the substance itself constituted inadequate replacement therapy. The findings at necropsy in 2 cases suggested congestive heart failure as the cause of death. Both clinical and chemical evidence indicated that excessive sodium and water were being retained and it appeared probable that the low potassium diet and the high intake of sodium salts were partially responsible for this retention. This suggestion was further strengthened by the studies of Tooke, Power and Kepler.[8] They showed that the patient who has Addison's disease has a normal response to salt deprivation and excess intake of potassium when treated with desoxycorticosterone acetate. This work indicated that the low potassium diet is at least superfluous if not dangerous.

The available evidence, therefore, suggested that the fault lay not with desoxycorticosterone acetate itself but with the manner in which it was being used. Treatment consequently was modified so that each patient who was given desoxycorticosterone acetate was also given a diet that contained an amount of potassium which was

equal to that in an average diet. The administration of sodium citrate was discontinued. Such a diet also permitted the intake of an adequate amount of protein and in addition eliminated the necessity of vitamin supplements.

Thirty-two patients having Addison's disease have been treated since these changes were made (Table 2). As has been mentioned previously, 14 of these patients had been treated with the low potassium, high sodium regimen. Thus far only one fatality has occurred. In this case the patient had a prolonged fever and a high sedimentation rate, possibly as the result of tuberculosis. Two of the patients who were getting along very poorly with desoxycorticosterone acetate and the low potassium, high sodium intake have been well since changing their diet. One of these patients has received implantations of pellets of desoxycorticosterone acetate on two occasions.

TABLE 2.—CONDITION OF PATIENTS TREATED WITH DESOXYCORTICOSTERONE ACETATE AND AN UNRESTRICTED DIET.*

| | Patients. |
|---|---|
| Dead | 1 |
| Able to be up and about but unable to work | 5 |
| Able to work most of the time | 10 |
| Able to work full time | 16 |
| Total | 32 |

* It is impossible at this time to compare this group as to survival rate, for none of these patients has received desoxycorticosterone acetate therapy longer than 20 months.

Sixteen of the 31 patients that are now being treated with desoxycorticosterone acetate are able to work every day and state that they feel well, 10 are able to work most of the time, and 5 are able to work occasionally. All the patients are instructed to take from 2 to 5 gm. of table salt daily. The daily dose of desoxycorticosterone acetate varies from 2 to 5 mg. and is taken hypodermically. The preparation is dispensed in sesame oil. The patients are urged to eat liberally and are advised to eat before retiring because of the possible danger of hypoglycemia. If the patient is unable to eat and the daily intake of potassium therefore falls below 4 to 5 gm., supplementary potassium in the form of potassium chloride tablets may be taken.

We still believe that the treatment of choice for Addisonian crisis is the administration of large amounts of cortical extract and intravenous injections of solution of sodium chloride to which sodium citrate is added. This form of treatment has the great advantage of producing effects promptly. After the crisis has been treated successfully, the administration of desoxycorticosterone acetate can be instituted. During periods of infection, cortical extract may be used in conjunction with desoxycorticosterone acetate. Whether such supplementary treatment is either necessary or advisable is a matter which we have to determine. The assumption underlying such a supplementary use of cortical extract is based on experimental evi-

dence which indicates that the administration of desoxycorticosterone acetate does not constitute complete replacement therapy. The usual cortical extract is comparatively weak in its capacity to cause retention of sodium and water and therefore can be given with comparative safety. If for any reason (usually economic) the patient cannot be treated with desoxycorticosterone acetate, treatment with the low potassium diet and a high intake of sodium salts is of value and remains the cheapest form of therapy.

In conclusion, we wish to emphasize the fact that desoxycorticosterone acetate, like insulin, is a two-edged weapon. It is a highly potent compound with the capacity of doing irrevocable damage when used indiscriminately. This dangerous potentiality is further increased if either the intake of sodium salts is too high or the intake of potassium too low. Here again the analogy to the relationship between the intake of carbohydrate and the dosage of insulin is apropos. The appearance of edema, rising blood pressure to hypertensive levels and evidence of a mounting venous pressure are danger signals which should warn the clinician to reduce the dose of both sodium chloride and desoxycorticosterone acetate. Finally, it should be remembered that the patient, when first treated with desoxycorticosterone acetate, is in a physiologic state that is entirely different from what it will be several weeks later after the disease has been controlled adequately. At first there is a marked deficit of sodium chloride in the tissues. Later the store of sodium salts and water has been replenished and in these respects at least the patient is in a physiologic state that approaches normal. When this approach to normalcy occurs the dose of desoxycorticosterone acetate should be reduced. If it is not reduced, the combined effects of a mounting blood pressure, a rising blood volume, a rising venous pressure and a weakened myocardium may vitiate an otherwise brilliant therapeutic result.*

**Summary.** Good results have been obtained in the treatment of patients who have Addison's disease by the use of desoxycorticosterone acetate and an unrestricted diet. If the patient cannot be treated with desoxycorticosterone acetate, treatment with a low potassium diet and a high intake of sodium salts is of value. However, the two types of treatment should not be combined. The

* Large doses of desoxycorticosterone acetate can be given to normal persons for short periods. Studies of the chemical composition of the blood will demonstrate the fact that retention of sodium and excretion of potassium have occurred. The healthy myocardium will tolerate these changes with impunity for a longer period than will the damaged myocardium. On the other hand, the patient who has Addison's disease does not have a normal myocardium. Furthermore, there is some experimental evidence that desoxycorticosterone acetate has much less effect on restoring muscle efficiency than it has in storing of salt and water. Under such circumstances, therefore, it is not surprising that rapidly progressive congestive heart failure with sudden death should occur. Such sudden deaths have often been attributed to hypoglycemia, but the available evidence in our opinion favors the view that in this instance, as in most others, sudden death implies failure of the heart.

treatment of choice for Addisonian crisis is the administration of large amounts of cortical extract and intravenous injections of solution of sodium chloride and sodium citrate.

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# BOOK REVIEWS AND NOTICES

BIRD MALARIA. By REDGINAL HEWITT, Sc.D., Department of Protozoology, School of Hygiene and Public Health, The Johns Hopkins University. (The American Journal of Hygiene Monographic Series, No. 15, July, 1940.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 228; 33 illustrations and 13 plates (1 in color). Baltimore: The Johns Hopkins Press, 1940. Price, $1.10.

FEW groups of parasites have been so extensively studied as have the plasmodia of birds; and the greater part of this work has occurred during the last 15 years. Whether or not results justify the effort is not the concern of this review. The various species of parasites of the genus Plasmodium that occur in birds are easily and conveniently studied in canaries and other avian forms that are adaptable to laboratory work. Certainly much has been learned and much remains to be learned of malaria in man. These parasites of birds have been and should continue to be convenient research tools in attaining a more complete understanding of the disease as it affects man. And to have the scattered publications on this subject collected and their contents analyzed and interrelated should be immensely helpful. The chapter headings indicate the contents: I. The Discovery and Early History of Bird Malaria; II. Geographical Distribution, Incidence and Host Records; III. Experimental Hosts and Methods; IV. Species of Bird Malaria Parasites; V. Characteristics of Laboratory Infections; VI. Symptomatology and Pathology; VII. Immune Reactions; VIII. The Effects of Drugs and Chemicals on Infections; IX. The Sexual Cycle and Mosquito Transmission; X. Exo-erythrocytic Stages Associated with the Life Cycle; XI. Problems for Investigation.

On the whole, the treatment of the subject seems adequate, and, although it is poorly written and repetitious passages occur, workers in this field will be indebted to Dr. Hewitt for this work. H. R.

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HANDBOOK OF ANÆSTHETICS (FORMERLY ROSS AND FAIRLIE). Revised by R. J. MINNITT, Trinity College, Cambridge, M.D. (LIVERPOOL), D.A. (R.C.P. and S. ENG.), Lecturer in Anæsthesia, University of Liverpool; Director of Anæsthetics, David Lewis Northern Hospital, Liverpool, etc. With Chapters on Local and Spinal Anæsthesia by W. QUARRY WOOD, M.D., CH.M., F.R.C.S.E., Surgeon, Edinburgh Royal Infirmary. Pp. 364; 102 illustrations. Fifth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $4.00.

THE value of a handbook of anesthetics would appear questionable in this country where anesthesia is chiefly given by nurse anesthetists who would not understand the text, or by trained physicians for whom it is too elemental. This may be too handsome a compliment for the new speciality of Anesthesiology, but there is no doubt of the aim of those interested in furthering physician-anesthetists.

Minnitt expresses his hesitancy in rewriting the Handbook completely at first, preferring to wait for enough time to elapse since the passing of his predecessor to make the task less delicate. One hopes he will persevere with his intention to "build a more thorough account of recent research in future editions."

To American anesthetists the book will be of interest because of detailed descriptions of equipment for administration of inhalation agents. The chapters on local and spinal anesthesia are sketchy, and there is even less on intravenous anesthesia.

The principles of anesthesia as expressed in the little volume are sound and are obviously those of an individual with wide experience in nitrous oxide, ether and chloroform anesthesia. Its value on this side of the Atlantic lies, therefore, in presenting to this country some of the ideas of English anesthetists—a function not without merit especially on the technical side.

R. D.

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THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students. By LOUIS GOODMAN, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and ALFRED GILMAN, PH.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. Pp. 1383; 126 figures and 67 tables. New York: The Macmillan Company, 1941. Price, $12.50.

THIS is by far the most important book on Pharmacology and Therapeutics that has appeared in many years. It is not merely a "re-write" of other texts, but an entirely new book written in a style that should make it interesting to medical students and clinicians alike. It contains a number of appealing features: an excellent historical section prefacing each chapter, doses that are not merely tabulated but discussed in detail in relation to clinical conditions, a good chapter on prescription writing, and at last a really complete index.

While great stress is laid upon practical considerations of therapeutics, theoretical aspects are discussed better than in any other standard text. This applies particularly to the section on the autonomic nervous system and its relation to drug actions. Other features meriting special praise are the chapters on the chemotherapy of syphilis, on the sulfonamides (100 pages), on digitalis, and on anesthetics. While the criticism may be made that the book is too long for student use, yet this Reviewer feels that it is certainly the finest Pharmacology book in the English language.

J. C.

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AMERICA ORGANIZES MEDICINE. By MICHAEL M. DAVIS, Chairman, Committee on Research in Medical Economics. Pp. 355. New York: Harper & Brothers, 1941. Price, $3.00.

THERE is a widespread conviction in this country that medical science and medical practice are of great service to national life as a means of raising the level of health, happiness and efficiency, and that this service is at present not as available as it should be to all the people. Although the expectations of medicine are often exaggerated by the public, it is clear to everyone that methods should be devised for a better distribution of medical care without lowering its quality.

There are many problems involved in devising such methods that will be acceptable to both the medical profession and to the public. These problems have been given years of study by the author of "America Organizes Medicine." The results of his study are now fully presented in a book impressive for its thoroughness, soundness and well-balanced discussion.

The subject of the organization of medicine is treated in three parts: The first part, "The Changing Shape of Things," deals with various problems of medical practice emerging from social and economic changes caused largely by the rapid expansion of medical knowledge, the inevitable develop-

ment of medical specialism and the demands of the public for an extension of medical care.

The second part of the book is concerned with the problems that have been encountered in efforts to organize medical service and methods of paying for it. The third part, "The Emerging Shape of Things," discusses the pros and cons of a few principles that seem essential for progress in the organization of medical care, and certain well-considered recommendations for action in this field are made. Many questions are raised throughout the book for which answers must be sought by the medical profession, by the lay public or in many instances by professional and lay collaboration.

The chapter on Federal Policies and State Legislation is of particular value as throwing light on some of the less understood and most widely discussed phases of medical organization, which have been the subject of prolonged arguments under the titles, "State Medicine" or "Socialized Medicine."

This book is an important and valuable contribution by an outstanding student of medical sociology and should serve to give a better understanding of the problems of medical care, of which both the medical profession and the public are in need. G. R.

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Diseases Transmitted From Animals to Man. By Thomas G. Hull, Ph.D., Director, The Scientific Exhibit, American Medical Association. Fourteen Contributors. Pp. 403; 43 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.50.

For this second edition Dr. Hull has been fortunate in obtaining collaborators who are recognized authorities in their particular fields of veterinary medicine and bacteriology, parasitology, virus diseases and public health. The plan of this edition is identical with that of the first. Section I (Diseases of Domestic Animals and Birds) contains new chapters on Louping Ill, Sore Mouth in Sheep, Equine Encephalomyelitis, Rift Valley Fever, and Fungous Diseases. In Section II (Rodent Affections) chapters on Typhus Fever and Relapsing Fever have been added. Pertinent references are appended to each chapter. The text is brief, concise and informative. It should continue to hold an important place in the literature of public health and preventive medicine. H. R.

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A History of Medicine. By Arturo Castiglioni, M.D., Formerly Professor at the University of Padua; Research Associate in the History of Medicine at Yale University. Translated from the Italian and Edited by E. B. Krumbhaar, M.D., Ph.D., Honorary President of the American Association of the History of Medicine. Pp. 1053; 443 illustrations. New York: Alfred A. Knopf, Inc., 1941. Price, $8.50.

The Krumbhaar translation of Castiglioni's History of Medicine represents an effective combination of unusual value for the teaching of medical history. Castiglioni published the first edition in 1927 in Padua, a University with a long background of notable scientific achievement. Inevitably the history, written primarily for an Italian audience, emphasized Italy's important part in the development of medicine. Some of the most brilliant advances had been made by Italians or with opportunities made available by Italy, as in the case of Vesalius and Harvey. On the other hand, continuing great movements have seldom been the result of the effort of any single group. The question of priority in the development of parts of the whole becomes a matter of interpretation. Therefore, a comprehensive treatment by two able historians with quite different training and differing point of view is valuable.

The English edition based on the second Italian edition of 1936 is not a mere translation. Much has been added and minor items in the original, chiefly of local interest, have been omitted. The result is a more balanced work brought up to date. Even the few years intervening between the Italian and English editions, with rapid development in chemotherapy and other branches of medicine, have called for certain special additions.

Both authors were obviously concerned over proper balance in presenting the different periods of medical history, a difficult task with the necessity of preserving a full account of origins, on the one hand, and giving comparable recognition to the significant achievements of later years, on the other. Who did more for the advancement of medical understanding, Celsus or Osler, Paré or the Mayos? How difficult it is to give to each his just proportion! All modern histories of medicine appear to hurry in the final chapters, and this is no exception. Yet as much space is given to the last century and a half as to the 2000 years between Hippocrates and Vesalius. Krumbhaar has added hundreds of details to the already comprehensive treatment of recent advances given by Castiglioni. A simple illustration, one of many that might be cited, is the short but accurate account of investigation on the vitamins, two pages, concisely written, covering accepted knowledge.

Recent developments in medical education, organization of research and publication of new knowledge are excellently treated. The brief section entitled "The Study and Practice of Medicine" has unusual importance for the student of trends in medical history. The history of medicine is not simply a catalog of the past, but a living record, providing clear indications for building on past success and clear implications for avoiding previous mistakes.

The style of the translation is fluent and vigorous. The printing is excellent. The illustrations have lost something in reduction from the larger size in the Italian edition, but are still first class. The general and subject bibliographies—considerably enlarged in this English edition—and the appended chronological list of universities and medical schools will be useful to students, investigators and historians. The longer subject index is a distinct improvement. Altogether the book is an important addition to American medical and historical literature. E. L.

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THE PRINCIPLES AND PRACTICE OF OPHTHALMIC SURGERY. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital, etc. Pp. 886; 451 engravings containing 1149 figures and 6 colored plates. Second Edition, revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

THE early appearance of the second volume of this textbook on ophthalmic surgery speaks for the splendid reception it has had. Very little new material has been added, but many of the unavoidable errors in the first edition have been corrected. It will continue to be a standard reference for ophthalmic surgery. F. A.

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DIETETICS FOR THE CLINICIAN. By MILTON ARLANDEN BRIDGES, M.D., F.A.C.P., Late Assistant Professor of Clinical Medicine and Lecturer in Therapeutics and Nutrition, New York Post-Graduate Medical School of Columbia University. Pp. 960. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

FOUR editions in 8 years bear eloquent testimony to the favor with which this book has been received by the profession. The work of 23 contributors, it is distinguished by excellent balance and arrangement, easy availability for quick reference, and its practical point of view. It is highly recommended to every physician and student. R. K.

THE DOCTOR AND THE DIFFICULT CHILD. By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M., Medical Director, London Child Guidance, Clinic and Training Centre. Pp. 214. New York: The Commonwealth Fund, 1940. Price, $1.50.

THIS little volume presents the fundamental principles and methods of child guidance for physician and medical student simply and clearly—also better than the vast majority of other books on the subject we have yet seen. The author, Medical Director of the London Child Guidance Clinic, is obviously a man of experience, sympathy and sound judgment. He makes no attempt to systematize the subject or group the well-known problems into strained categorical headings. Dr. Moodie opens with a "recognition of the problem," follows with a simplified but very useful chapter on the study of cases including histories and then proceeds with a section on evaluation of syndromes and general methods of treatment. There is then a more complete discussion of 18 specific behavior problems and psychoses.

The book is rather informal but that contributes to its value to the average physician. It is not a scientific treatise in the usual sense of the word, but is packed with timely, sound advice and common sense solutions to routine maladjustments. The Reviewer has been looking for a book like this to recommend to medical students and internes. E. T., JR.

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THE STORY OF CLINICAL PULMONARY TUBERCULOSIS. By LAWRASON BROWN, M.D., Late Director of Trudeau Sanatorium; Lecturer in Trudeau School of Tuberculosis. Pp. 411; 1 illustration. Baltimore: The Williams & Wilkins Company, 1941. Price, $2.75.

THE lectures on the history of tuberculosis given by the author at the Trudeau School form the basis for this posthumous collection of essays. The development of ideas concerning the diagnosis and treatment of phthisis is shown in a series of "visits" with physicians in 1700, 1800 and 1900. Interest is centered chiefly on physical diagnosis, and the central figure of the book is Laennec. The spread of use of auscultation and percussion through Europe and the United States is traced in detail, and brief accounts are given of the development of roentgenologic diagnosis and of artificial pneumothorax and surgical collapse therapy. Physicians and surgeons especially interested in diseases of the chest as well as those interested in medical history will be delighted by this book, but everyone who uses the stethoscope, whether he be practitioner or student, will profit by acquaintance with this fascinating excursion into the relatively recent past. Readers of this journal will find particular interest in the final chapter, in which the author lists and discusses the articles on auscultation appearing in English and American medical periodicals before 1850. Foremost among these in the number of noteworthy contributions was the AMERICAN JOURNAL OF THE MEDICAL SCIENCES H. I.

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ESSENTIALS OF DERMATOLOGY. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University; Assistant Dermatologist, Firmin Desloge and St. Mary's Hospitals; Visiting Dermatologist, St. Louis City Sanitarium and Isolation Hospital. Pp. 407; 143 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $4.75.

DR. TOBIAS has presented a valuable addition to the growing list of handbooks of dermatology for the student and general practitioner. In spite of the small size of the book, the author has in inimitable style condensed the essentials of dermatology without giving the reader the feeling

of reading a series of telegrams. In addition, the illustrations are well chosen and for the most part are well reproduced.

Although intention is expressed of discussing as far as practical each disease from the standpoint of internal medicine, the author does not stress the need for general physical examination in evaluating a dermatosis, for example. One other criticism is the inclusion of many rarities in a book on essentials. This is apparently done at the sacrifice of detail in some places, such as in the discussion of various diagnostic intradermal tests. It hardly seems advisable, moreover, to recommend for the general practitioner any arsenical antisyphilitic agent for a patient who has once suffered an arsenical dermatitis. (*Cf.* p. 82, where mapharsen is recommended after such an event.) On page 298, the histologic section (Fig. 90) labelled "senile keratosis" seems to the Reviewer to be good for seborrheic verruca (seborrheic keratosis).

Among the commendable features of this book are: specific statements regarding the general practitioner's limitations in handling various dermatoses—*e. g.*, gold compounds and Roentgen ray in lupus erythematosus; the modern viewpoint in the discussion of most conditions, especially eczema and dermatitis; excellent differential diagnostic tables; and the list of general therapeutic suggestions at the end of the book.

On the whole, the Reviewer unhesitatingly recommends this book for the student and the general practitioner who does not have the facilities nor the inclination to consult a larger volume. H. B.

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HERNIA. By ALFRED H. IASON, B.A., M.D., Consulting Surgeon, Long Beach Hospital; Director of Surgery, Brooklyn Hospital for the Aged; Surgeon, Manhattan General and Madison-Park Hospitals, etc. Pp. 1325; 355 illustrations by ALFRED FEINBERG, Instructor of Medical Illustration, Department of Pathology, College of Physicians and Surgeons, New York City. Philadelphia: The Blakiston Company, 1941. Price, $15.00.

THIS large volume is presented in three sections: 1, Historical Evolution of Hernial Surgery; 2, Technical Aspects; 3, Medico-Legal Aspects. The introduction to this volume begins with a blistering attack on operators (which the author calls surgeons) and their practices "down to the mid-nineteenth century." He soon develops an evangelical fever in his method of presentation. The statements which he makes, while perhaps true, are dramatized to the extent of losing much of their effectiveness. Much of what is reviewed has nothing to do with herniæ. The descriptions of various older operative techniques are interesting and worthwhile from a historical viewpoint.

The statistical data are thoroughly presented, more so than is necessary, and the same can be said for many other sections of the book. No other volume on this subject presents the various subjects in so detailed a manner. It is in fact a work of reference rather than a monograph which surgeons will pick up and read from cover to cover.

Some of the discussions which are given under the section on treatment hardly belong in this volume. The suggestion that Lugol's solution be used to prepare thyrotoxic patients for operation for hernia demonstrates a lack of the relative importance of two surgical problems. Why status lymphaticus, diabetes mellitus, shock, and a large group of hepatic function and other tests should be described at length in this volume is not apparent. The paragraph on Hepatic Insufficiency on pages 444 and 445 is filled with inaccuracies. What possible use calcium chloride can have in hepatic insufficiency or acidosis, or even hemorrhage in jaundiced patients, is beyond the Reviewer's knowledge. Bleeding and coagulation times are not nearly

so useful as is the prothrombin time in determining the hemorrhagic tendency in jaundiced patients. Nor is there the slightest evidence that "It is this fat content—among other substances—which protects the tissues from injury due to volatile anesthetics." This section of the book could have been eliminated for it not only does not add to the usefulness of the volume but detracts from it because of gross inaccuracies.

The descriptions of the operations and the illustrations are good, but too many techniques are described. If this volume were rewritten and condensed to about one-third its present size it might be well received.

I. R.

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RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 432; 67 illustrations, including 3 plates. Fourth Edition. Philadelphia: The Blakiston Company, 1940. Price, $5.00.

IN spite of the title, this book is not limited to recent advances but gives an extensive survey of the present state of our knowledge in the field of endocrinology, dealing not only with recent reports but with fundamentals long ago established. Consequently, no special knowledge on the part of the reader is presupposed. The word "recent" is often applied to findings of 10 to 18 years ago, a period which is relatively old in this field. Probably this is accounted for by the wording of the first edition which has not been modified in this the fourth edition.

As the author is a biochemist, the discussion is more critical and authoritative when the chemical aspects of hormones are discussed. A lack of first-hand knowledge of morphologic changes is occasionally apparent. There seems to be an undue emphasis placed on British and Canadian sources, especially in regard to structural changes not generally accepted by pathologists. It seems to the Reviewer that this book could be improved by omitting mention of some reported findings that have not been substantiated and that no longer seem to be of interest even as possibilities.

On the whole, however, the book contains a fund of facts, systematically arranged, and clearly and simply stated, which serves a useful purpose in enabling practitioners and students to find readily available references to literature in a specialized field of science.

I. Z.

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ORAL PATHOLOGY. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery, and CHARLES A. BRACKETT Professor of Oral Pathology, Harvard University. Pp. 1306; 1370 illustrations, including 137 in color. St. Louis: The C. V. Mosby Company, 1941. Price, $15.00.

THE author's well-known previous texts on dental pathology, diagnosis and treatment planning are climaxed by his *Oral Pathology*. This volume represents the most recent, extensive and detailed presentation of this subject. Those interested in referring to review articles or original source material will appreciate the extensive bibliographies included at the end of each chapter.

The chapters on dental caries, periodontal disease, the nutritional and endocrine aspects of normal and abnormal dental development afford a thorough review of the past work and current opinions in these fields. The author's experience and interest in the diseases and tumors of the jaws make these chapters the most interesting, authoritative and valuable of any in the book.

Patterned after his *Clinical Pathology of the Jaws*, the clinical, histo-

pathologic, roentgenologic findings and treatment are presented in detail. The numerous illustrations, which are one of the features of this text, contribute materially to a more complete understanding of the disease. The clinical appearance, the histologic and roentgenologic findings are illustrated for most of the diseases. Many of the photomicrographs and some of the clinical pictures are reproduced in color.

The common and uncommon diseases of the oral mucosa, lips and tongue are also discussed. The organization, completeness and authoritativeness of this section, for the most part, is not in keeping with the rest of the volume. No mention is made of the pathogenesis of some of the diseases, although the etiology is given; in others the pathogenesis is given in detail but no mention is made of the etiology. The colored figures (50 in number) illustrating this section are for the most part the best the Reviewer has seen. They comprise a valuable atlas covering this phase of oral pathology.

Adequate indexing of such an extensive work is a difficult task, yet a necessary feature in a reference text. More extensive cross-indexing would be desirable. It required several minutes to locate the text dealing with mixed tumors of the parotid gland. The Reviewer had occasion to look up syphilitic rhagades. This subject was not indexed. The indicated text on congenital syphilis made no reference to this condition or to Hutchinsonian teeth. The latter subject was indexed but no mention was made of the other symptoms of congenital syphilis. The text relating to this subject is found in four widely separated parts of the book, some without representation in the index. Keloids or Mikulicz's disease are not found in the index although a description of the latter disease is included in the text. These minor criticisms in no way lessen the reading value of the book, but do limit its usefulness as a reference source.

Thoma's *Oral Pathology* would be a valuable addition to any medical or dental library. It would be particularly useful to those interested in oral pathology or those interested in the clinical manifestation of oral pathosis. The publisher is to be complimented on the typography, the general excellence of the illustrations and the substantial binding. L. B.

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UNIVERSITY OF CALIFORNIA HOSPITAL FORMULARY AND COMPENDIUM OF USEFUL INFORMATION. Pp. 270. Berkeley, Calif.: University of California Press. 1941. Price, $2.00.

IN addition to the University of California Formulary with practical information on prescription writing, vehicles and many useful prescriptions, this work includes other valuable data such as emergency treatment and description of standard procedures in the medical, pediatric, dental, Roentgen ray and laboratory services. The book is well printed on thin paper, so that it is compact despite the wealth of material contained. It should prove to be a very convenient source of information to medical students, internes and practitioners. J. C.

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AN INTRODUCTION TO MEDICAL SCIENCE. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology and Bacteriology in the University of Toronto, Toronto, etc. Pp. 358; 124 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $3.50.

AFTER 4 years, Dr. Boyd offers a second edition of this useful book. It is 42 pages longer and contains 16 more engravings, the changes being made "with the object of making the book of greater value to the nurse commencing the theoretical side of her training. There is a new historical chapter outlining the development of medicine from its early beginnings to its most recent triumphs. The chapter on bacteriology has been rewritten and

greatly amplified, including illustrations of all the common disease-producing bacteria. . . . . New sections have been added on the clinical and laboratory methods used in the detection of disease, the uses of *x*-rays and radium, the vitamins, jaundice, pyelonephritis, purpura, agranulocytic angina, and the new wonder-working agents of chemotherapy." We repeat the views intimated in the review of the first edition of this book that it represents what an Introduction should be and is not to be confused with meretricious short-cut compends designed merely to help the parrot student "get by" his exams. We are glad to see retained in the considerably changed Preface of this edition the useful aphorism: "A little knowledge is a dangerous thing, but not if you know how little it is." E. K.

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THE PHARMACOLOGY OF ANESTHETIC DRUGS. A Syllabus for Students and Clinicians. By JOHN ADRIANI, M.D., Instructor in Anesthesia, New York University College of Medicine; Assistant Visiting Anesthetist, Bellevue Hospital. Pp. 86; illustrated. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, $3.50.

THIS small volume contains a great deal of information in outline form for those interested in the new field of Anesthesiology. Isolated facts in a variety of subjects are made readily available; the presentation is clear and there is a lengthy bibliography.

It is difficult to recommend this syllabus-type of work to one interested in reading for its own sake. The book can, however, be recommended to those preparing for examinations as well as to those organizing a teaching program. R. D.

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START TODAY! YOUR GUIDE TO PHYSICAL FITNESS. By C. WARD CRAMPTON, M.D., Major, Medical Reserve Corps, United States Army; Formerly Director of the Department of Physical Education and Hygiene, New York Board of Education, etc. Pp. 224; illustrated. New York: A. S. Barnes & Co., 1941. Price, $1.75.

WE agree entirely with the Preface to this book written by Alexis Carrel: "Today, more than at any other time of history, we need men who are physically and mentally fit. But physical fitness must not be separated from mental fitness. In his conception of physical fitness, Dr. Crampton includes not only the training of the muscles, but also that of the organs and of the mind. He aims at developing the whole individual, as well as his motor system, his glands, and his consciousness. Ultimately, man in the fullness of his virility. I am happy to recommend this most useful book to the men of America." E. K.

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## NEW BOOKS.

*Elimination Diets and the Patient's Allergies.* A Handbook of Allergy. By ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, San Francisco, Calif.; Consultant in Allergic Diseases, Alameda County Hospital, Oakland, Calif. Pp. 264. Philadelphia: Lea & Febiger, 1941. Price, $3.00.

*Play for Convalescent Children in Hospitals and at Home.* By ANNE MARIE SMITH, Staff Instructor, Leaders' Training School, Community Recreation Service, Chicago, Ill. Pp. 133. New York: A. S. Barnes & Co., 1941. Price, $1.60.

*Start Today!* Your Guide to Physical Fitness. By C. WARD CRAMPTON, M.D., Major, Medical Reserve Corps, United States Army; Formerly Director of the Department of Physical Education and Hygiene, New York Board of Education, etc. Pp. 224; illustrated. New York: A. S. Barnes & Co., 1941. Price, $1.75. (Review above.)

*Life and Death at Low Temperatures.* (No. 1 of a series of monographs on general physiology, edited by B. J. LUYET.) By B. L. LUYET, Professor of Biology, and P. M. GEHENIO, Instructor in Biology, Saint Louis University. Pp. 341; 33 illustrations. Normandy, Mo.: Biodynamica, 1940. Price, $4.50.

*Optical Activity and Living Matter.* (No. 2 of a series of monographs on general physiology, edited by B. J. LUYET.) By G. F. GAUSE, Professor of Experimental Biology, University of Moscow. Pp. 162; 18 illustrations. Normandy, Mo.: Biodynamica, 1941. Price, $2.75.

*Orbital Tumors.* Results Following the Transcranial Operative Attack. By WALTER E. DANDY. Pp. 168; 100 illustrations. New York: Oskar Piest, 1941. Price, $5.00.

*Berkeley Moynihan, Surgeon.* By DONALD BATEMAN. With a Preface by LORD MOYNIHAN. Pp. 354; illustrated. London: MacMillan & Co., Ltd., 1941. Price, $4.00.

*Clinica del Trabajo.* Revista Mensual de Profilaxis y Seguridad, Vol. 1, March and April, 1941. Director General DR. OSCAR RODRIGUEZ REY; Forty-one Collaborators. Pp. 34. Buenos Aires, 1941.

This new monthly review from the Argentine is a welcome addition to the journals on Hygiene and Social Medicine.

*The Precipitation of Clinical Symptoms.* Pp. 45 (Lithoprinted); 27 illustrations. (Reprint of Chaps. II and III of Vol. IV, Part 1 of "The Patient and the Weather," by W. F. PETERSEN and M. E. MILLIKEN.) *Vascular Disease.* Pp. 129; 64 illustrations. (Reprint of Chap. V, of Vol. IV, Part 1.) *Blood Dyscrasia.* Pp. 222; 112 illustrations. (Reprint of Chap. IV, of Vol. IV, Part 2.) Ann Arbor, Mich.: Edwards Brothers, Inc.

These subjects are reprints from Volume IV of a series comprising 3205 pages and 1724 illustrations. The monograph is a masterpiece of research work that appeared during 1934, 1935, 1936 and 1937. As each of the four volumes was received it was given a careful review.

## NEW EDITIONS.

*An Introduction to Medical Science.* By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology and Bacteriology in the University of Toronto, Toronto, etc. Pp. 358; 124 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $3.50. (Review p. 279.)

*Accidental Injuries.* The Medico-Legal Aspects of Workmen's Compensation and Public Liability. By HENRY H. KESSLER, M.D., PH.D., F.A.C.S., Medical Director, New Jersey Rehabilitation Clinic; Formerly Medical Advisor, New Jersey Workmen's Compensation Bureau, etc. Pp. 803; 202 illustrations. Second Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

*The American Illustrated Medical Dictionary.* A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., LIEUT.-COL., M.R.C., U. S. Army; Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association, etc., with the Collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1647; 914 illustrations, including 269 portraits. Nineteenth Edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1941. Price, $7.50.

The 19th edition of this standard work includes more than 2000 new words, covering all departments of medicine and related sciences. Many of them are defined for the first time in the present edition of this book, undoubtedly the leader in its field.

# PROGRESS
OF
# MEDICAL SCIENCE

## SURGERY.

UNDER THE CHARGE OF
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### DISEASES OF COLON AND RECTUM.*

In this review the subject of proctologic disease has been dealt with from a broad point of view. The discussion is confined to the local anorectocolonic disease without systemic involvement; to primary local disease with secondary involvement of distant regions, and to local disease as an expression of systemic disease.

**Neoplastic Disease.** Recently, all phases of polypoid disease of the rectum and colon have been extensively studied.[5,25,26,33b,62,78,99,133] The term polyp as used by most writers refers to single or multiple pedunculated or sessile adenomas. Small islets of hyperplasia of the epithelium of the rectum and sigmoid are believed to be precursors of polyps. The great clinical significance of polypoid disease lies in its frequency of progression to malignancy. It is also believed that the polyps encountered in association with chronic ulcerative colitis may undergo adenomatous and malignant changes.[25] This is a clear-cut example of the transition from inflammatory hyperplasia of the mucosa of the bowel to the intermediary adenoma and finally to frank carcinoma.

The purpose of the treatment is the destruction of the polyps and the islets of epithelial hyperplasia by fulguration. This procedure is not without risk even in the hands of the expert operators. To prevent serious complications such as perforation or hemorrhage, it is best to err on the side of conservatism[129] and to complete the fulguration in more than one sitting. Polyps occurring above the reflection of the peritoneum should be treated in a hospital; those present below the peritoneal reflection may be fulgurated in the office. Polyps of the colon situated beyond the safe reach of the sigmoidoscope are best removed by a transcolonic procedure.[20,104]

* From the Division of Proctology, Department of Surgery, Ernest K. Tanner, Chief Attending Surgeon, The Brooklyn Hospital, New York.

Multiple polyposis or adenomatosis is a heredofamilial, and perhaps a congenital, disease which nearly always undergoes malignant changes during the first three or four decades of life.[89,91] Because of the widespread involvement of the colon, a colectomy in graded operations is indicated. In the absence of malignant changes of the rectum, the rectum may be saved in those instances where complete destruction of the polyps of the rectum and rectosigmoid by fulguration is possible. Following this procedure, an anastomosis of the ileum to the upper rectum or the lower sigmoid is made which is subsequently followed by a subtotal colectomy. Recurrent polyps of the rectum can easily be refulgurated.

As already inferred, adenocarcinoma of the rectum in many cases develops from previously benign polyps and may grow by extension on the mucosal surface and by invasion of the wall of the bowel.[41] Then the spread occurs into the perirectal fat, and later upwards along the superior hemorrhoidal lymphatic pathway.[26,55,56] When the lymphatics become blocked, retrograde and lateral spreads occur. The Miles type of combined abdominoperineal resection of the rectum with high ligation and division of the superior hemorrhoidal blood-vessels offers the best means for the radical removal of the rectal lesion and the involved perirectal tissues, mesentery and the high lying lymph glands.[58,74,107,125] Whenever the neoplasm is near the level of the levator ani muscles, these structures should be excised widely because metastases occur along these muscles.[56] The perineal excision of the rectum with colostomy, such as described by Lockhart-Mummery, being a less formidable procedure than the abdominoperineal resection, is reserved for the extirpation of low rectal malignancies in patients who constitute poor surgical risks because of either advanced age or concomitant disease.

Surgical diathermy may be used for the treatment of advanced and inoperable cases of cancer of the rectum.[135] Surprisingly good results are observed in the occasional patient following this form of treatment. Fulguration has also been successfully employed for the treatment of early papillary adenocarcinoma of the rectum which is not fixed to the submucosa and the muscles of the rectal wall. In suitable cases, surgical diathermy may be combined advantageously with radium and followed by Roentgen irradiation.[134]

For carcinoma of the colon, an ingenious and important procedure of temporary double-barrel colostomy with the purpose of isolating, defunctionalizing and debacterializing the colon distal to the colostomy has recently been described by Devine[37] and modified by Ochsner, DeBakey and Rothschild.[113] In this defunctionalizing colostomy the two ostia are separated widely to prevent fecal contamination of the distal stoma and the isolated bowel. Following the successful resection of the tumor-bearing colon and the healing of the anastomosis, the continuity of the bowel is reëstablished by the use of a specially designed colostomy clamp.

The details of the management and the complications of permanent colostomy have recently been described.[40,128]

The present-day superior results following colonic and major rectal surgery are largely due to the various operative technical refinements, the frequent transfusions of blood, the restoration of the normal balance of fluid, electrolytes and protein, and the administration of vita-

mins and of other essential substances of which the body may be deficient or depleted. Sulfanilamide administered preoperatively and postoperatively (or deposited in the peritoneal cavity at the conclusion of the operation) has aided in reducing the incidence of postoperative peritonitis. Sulfanilamide apparently exerts a bactericidal effect on the *Strep. hemolyticus* which is frequently isolated from the retroperitoneal tissues, the wall of the bowel, or on the mucosal surface of the neoplasm,[53] and a bacteriostatic effect on other organisms causing peritonitis.[90] A more recent study of the effect of sulfanilamide, sulfapyridine and sulfathiazole on experimentally produced *E. coli* infections in mice showed that sulfathiazole was the most effective of the sulfonamides.[80] On the basis of the results of this study, it was suggested that sulfathiazole be employed for the treatment of *E. coli* infections in man as well as for prophylactic purposes following operations upon the colon.

**Diarrheas.** A recent important study[79,117] showed that diarrhea may occur as a postoperative complication in severely ill patients who have been in shock as a result of an operative procedure. This diarrhea is often caused by multiple focal colonic ulcerations which arise on a vascular basis. They have been explained by the assumption of a vasospasm which occurs as a compensatory vasomotor response in shock and have been reproduced by the experimental production of vasospasm.

*Bacillary Dysentery.* The recognition of acute bacillary dysentery is relatively simple. It has however not yet been established how long the dysentery organisms may remain active in the host and what percentage of acute cases lapse into chronicity.[138c] In chronic bacillary dysentery and in carriers, the recovery of the specific organisms, especially the Flexner bacillus, is difficult because of the intermittency of excretion of these organisms.[47] The administration of acidophilus milk is said to facilitate the recovery of the late lactose fermenters of Duval-Sonne.[127] The very recently improved culture media, *e. g.*, bacto bile salts (Difco), are said to be as specific for dysentery organisms as bismuth media are for the typhoid bacillus.

It is known that healthy individuals who give no history of an antecedent bacillary dysentery infection or digestive disturbance may harbor *B. paradysenteriæ*.[15] Apparently factors other than the presence of dysentery organisms are essential for the production of clinical manifestations of bacillary dysentery infections. It is possible that a qualitative *E. coli* deficiency may be of etiologic importance in bacillary dysentery. Utilizing Nissle's studies of the antagonistic index between *E. coli* and *Eberthella typhi*, Maner[31] found "that Escherichia coli isolated from dysentery stools are invariably deficient in antagonistic characters, in all cases the symptoms being associated with a qualitative Escherichia coli deficiency." Vitamin deficiencies may be another important factor responsible for the clinical manifestations of bacillary dysentery. It has been shown that a diet deficient in vitamin A[142] and in certain components of vitamin $B_2$ complex produces manifestations of bacillary dysentery in monkeys that were known to be carriers of *B. paradysenteriæ*, Flexner.[71]

The acute form of bacillary dysentery is self-limited, hence the efficacy of any therapy in this disease is difficult to evaluate. Pectin, substances containing pectin and bananas have been used exten-

sively.[85,114,146,152,153] Sulfanilamide and its derivatives have been employed with encouraging results in experimental animals and in a number of clinical cases of bacillary dysentery.[73] Recently, during a pharmacologic study of the various sulfanilamide derivatives, Marshall *et al.*[96] encountered several highly antibacterial compounds which are water-soluble and yet poorly absorbed from the gastro-intestinal tract, making it possible to produce a high concentration of the drug in the intestine and a low concentration in the blood and tissues. One of these compounds was designated as sulfanilylguanidine. The application of this new principle to bacterial chemotherapy appears to be ideal for the treatment of acute bacillary dysentery and other bacterial infections that are predominantly or entirely localized in the intestine.

Transfusions of blood from artificially immunized donors for the treatment of chronic bacillary dysentery has been suggested.[138d] The practical results obtained and the theoretical basis of this method of therapy justify the continuation of immunotransfusion therapy. Autogenous vaccines also have a definite place in the therapy of chronic bacillary dysentery.

*Chronic Ulcerative Colitis.* Little has been advanced to clear up the existing confusion regarding the etiologic agent. Howard[67a] and Kessel[75] question the etiologic rôle of Bargen's diplostreptococcus in chronic ulcerative colitis. Many investigators believe that a number of cases of chronic ulcerative colitis are a form of chronic bacillary dysentery.[138c] A belief is also current that chronic ulcerative colitis is due to a yet unidentified organism (virus?) or to allergy in a certain number of cases.

The evaluation of any form of therapy in this disease is difficult because of the natural tendency for remissions and exacerbations. The prime object of the present-day medical treatment of chronic ulcerative colitis is the restoration of the grave nutritional deficiencies by the administration of adequate doses of all vitamins[6,92] and especially of vitamins B complex and C, liberal transfusions of blood and frequent feedings of bland, nutritious foods with an excess of protein. The rectal instillation of cod-liver oil is a useful adjuvant in the treatment of the subacute and chronic cases.[9,131b] Although sulfanilamide and its derivatives have not yet been given a sufficiently extensive trial to permit definite conclusions, this form of chemotherapy already shows promise.[14,27]

In extremely ill patients with acute exacerbations of chronic ulcerative colitis, remissions can frequently be produced by the administration of antitoxic *B. coli* horse serum (Winkelstein). This form of therapy is still in the investigative phase.

Ileostomy should be performed when adequate medical treatment is failing. The mortality from this operation is decreased if intraperitoneal exploration and manipulation of the colon is avoided at the time of ileostomy.[52] After a lapse of time, when the patient's general health is restored, colectomy in graded operations may be performed.[21] Unless severely involved by perirectal suppurations and fistulas and polypoid degeneration, it may be possible to preserve the rectum in anticipation of a future ileoproctostomy.[52]

Polyposis, stricture, anal abscess and fistula, and anal fissure are the important proctologic complications of chronic ulcerative colitis. During the active phase of the colonic disease, all anorectal complications

should be treated palliatively except for abscesses which should be drained. Fistulectomy should be avoided because anal incontinence frequently follows this operation.[130]

*Amebic Dysentery.* Amebic infection is pandemic in the temperate zone. The incidence of amebiasis in various parts of the United States exceeds 10% or is about 10 times greater than the incidence of active tuberculosis.[24] Amebic infestation is generally transmitted by infected food handlers.[124]

A comprehensive study of infestation of the colon with *Endamœba histolytica* and other protozoa and parasites includes a proctosigmoidoscopic survey, a microscopic examination of the feces and the scrapings from the inflamed mucosa or the surface of the ulcers. The granulomatous masses in the rectum should be studied histologically as they may either simulate or accompany malignant disease.[22,39] A roentgenogram of the colon with the aid of barium sulphate should never be omitted because it may demonstrate additional granulomas in other parts of the large intestine, especially in the cecum. The complement fixation test has not yet attained universal acceptance because of the non-inclusiveness of the results; it is still of adjunctive rather than of primary value.[116a]

Recently good results have been reported following the employment of a combination of carbarsone administered by mouth and chiniofon administered intrarectally as small retention enemata.[100] Intracolonic heat supplied by means of colonic irrigation with 1 to 5000 copper sulphate solution at a temperature varying from 45° to 47° C. has also been recommended.[36] It should however be realized that the eradication of the parasite following anti-amebic therapy does not always relieve the digestive complaints in many patients. In the absence of amebæ, these abdominal symptoms can be controlled by sedatives and antispasmodics, although they may recur after non-specific therapy has been discontinued.[67b,116b]

The intestinal lesions in amebiasis requiring surgical treatment are: appendicitis, perforation with resulting peritonitis, massive hemorrhage, amebic granulomas, cicatricial stenosis and pseudopolyposis. The extraintestinal lesions include abscess of the liver, pleuropulmonary amebiasis, cerebral abscess, cutaneous ulcerations and abscess, abscess of the spleen and urogenital involvement.[112]

*Mucous Colitis.* "Mucous colitis" is very probably merely an expression of or a somatic response to nervous tension, such as anxiety, resentment and guilt.[147] Since inflammation of the colon is absent in "mucous colitis," this term should be abandoned, especially in view of the fact that by long usage the genetive ending "itis" has come to connote inflammation.

The mucosal changes observed during an attack of "mucous colitis" can to a degree be reproduced either by the topical application of pilocarpine or physostigmine to the colonic mucosa or by the oral administration of various drugs of the choline group to normal individuals.[147] These drugs exert their effect through the action upon the parasympathetic fibers of the autonomic nervous system.

The etiologic rôle of allergy has been established in some cases of "mucous colitis." This phase of the problem has to date been insufficiently studied.

**Diverticulosis and Diverticulitis.** Diverticula are usually acquired. In many cases the diverticula are of congenital origin which develop only in the presence of factors that make for the production of an acquired diverticulum (Beer). Asymptomatic diverticula are frequently encountered during the routine Roentgen ray examination of the colon with the aid of barium sulphate or during incidental abdominal operations;[61] the presence of diverticula is not suspected unless a pathologic process sets in.[42] The onset and the early course of diverticulitis may resemble acute appendicitis. Diverticulitis responds well to medical treatment in over 90% of the cases but requires prolonged medical supervision. The complications of diverticulitis consist of perforation with abscess, acute perforation with peritonitis, peritonitis without perforation, perforation high in the rectum with consequent ischiorectal or ischioanal suppurations, pericolitis with peridiverticulitis and thickening of the bowel wall eventuating in partial or complete obstruction of the bowel, enterocolic or vesicolic fistulas and cancer. These conditions invariably require surgical intervention.[4,16b]

There is considerable uncertainty as to what extent diverticulitis is incidental or etiologically directly contributory to the rare occurrence of cancer in the diverticular pouches.

**Tuberculosis.** The presence of viable or virulent tubercle bacilli in the terminal bowel in many cases of pulmonary tuberculosis with positive sputa causes contamination of the anorectal tissues.[97,98] Hence the finding of tubercle bacilli by culture or animal inoculation is not significant in the study of the anal lesions in these patients. In contrast, the cultures and animal inoculation are conclusive in the study of anorectal lesions of patients with pulmonary tuberculosis who have negative sputa. The presence of tuberculosis in the anorectal granulation tissue on histologic examination is therefore an essential criterion for the diagnosis of a tuberculous anal lesion in the cases of active pulmonary tuberculosis with a positive sputum.[97] On a single section this is only positive in about 50% of the cases, but when run in serial section it is at least 75% positive.[97] In many cases a diagnosis of anorectal tuberculosis can be made clinically by the characteristic appearance of the anal lesion.[94]

Anal fistulas and preëxisting suppurations occur about 10 times as often among the tuberculous as among the non-tuberculous patients; these anal lesions are encountered more often in patients with advanced than with early pulmonary tuberculosis and are less prevalent in private than in ward practice.[94]

The cure of the tuberculous anorectal lesion demands radical surgical extirpation and meticulous postoperative care. Healing after operations is protracted in the patient with pulmonary tuberculosis who has a positive sputum and is but slightly retarded in the patient with negative sputum. In either case healing is complete following adequate surgical treatment which is augmented by measures aiming to improve the general health of the patient.

**Venereal Diseases.** *Venereal Lymphogranuloma.* This is a systemic disease with localized manifestations in the inguinal region, genital tract and the anorectocolonic tube.[11,83b] The intestinal lesions consist of proctitis, colitis, suppurations, fistulas *in ano*, rectovaginal fistulas and stricture. The rectal strictures may be tubular or diaphragmatic

in character. Strictures and other rectal complications occur more often in women as a result of the spread of the virus through the direct lymphatic communication from the cervix, the posterior vagina and the fornices to the lymph glands in the pelvis and thence to the pararectal glands, producing perirectal infection and fibrosis. Women with primary lesions on the vulva usually develop bubos because these genital structures are drained by the superficial lymphatics to the inguinal lymph glands. Inguinal adenitis or bubo is believed to act as a barrier to the spread of the virus to the pelvic and pararectal lymph glands. In men, the occurrence of bubos is very common and rectal involvement infrequent because most of the lymphatic drainage from the external genitalia is predominantly superficial to the inguinal lymph glands. In the absence of an antecedent bubo or inguinal adenitis, anorectal complications in men are the result of the direct spread of the virus from a lesion in the posterior urethra to the pararectal lymph glands, or from the inguinal nodes through the femoral and inguinal canals into the endopelvic fascia and glands. Primary infection and the resulting proctitis and stricture may be brought about by anal coitus or by the use of contaminated enema tips.

A positive intracutaneous Frei test usually establishes the diagnosis of venereal lymphogranuloma. However, the finding of the virus in the bowel discharges or tissues constitutes positive proof that the virus is the cause of the intestinal lesions.[115b]

Sulfanilamide, sulfathiazole, or Frei antigen are effective therapeutic agents exerting profound beneficial systemic as well as local effects.[83a,95] Sulfanilamide and sulfathiazole, because of their universal availability, appear to be the drugs of choice. The beneficial systemic effects are evidenced by the disappearance of fever and leukocytosis, the rise of the hemoglobin values, the reversion of the hyperglobulinemia toward the normal level[123] and the restoration of a sense of well-being. Chemotherapy produces a diminution, if not the total disappearance, of the perirectal infiltration and the exudate; the raw surfaces heal, and the rectal fibrous strictures become more easily dilatable[95] although sulfanilamide and sulfathiazole have no direct influence upon scar tissue. Since the institution of chemotherapy, surgical treatment of the anorectocolonic manifestations of venereal lymphogranuloma has been largely limited to incision and drainage of localized perianal and perirectal suppurations, to the performance of an occasional temporary colostomy for acute obstruction and the digital or instrumental dilatation of the fibrous strictures.

To obtain the best results and the maximum of safety, especially during the intensive phase of treatment, chemotherapy should be instituted in a hospital.[95] These patients, like those with other venereal diseases, are notoriously unreliable and it is dangerous to entrust potent drugs to them without proper daily medical supervision. Early toxic symptoms may go unrecognized as they are unpredictable.

Recently, intrarectal diathermy combined with Frei antigen was proposed for the treatment of rectal stricture.[101]

*Gonorrhea.* In man, anal gonorrhea is usually acquired through pederasty. Except for cases of anal intercourse, contamination in girls and women is believed to take place during the act of defecation when a simultaneous expulsion of gonococci-laden discharge from the vagina

and a normal eversion of the anal mucous membrane occurs. Suitable biologic conditions for the acquisition and maintenance of gonorrheal infection are furnished by the transitional epithelium of the intermediate zone of the anal canal, the anal ducts and the crypts of Morgagni. The infection may spread to the deeper perianal and perirectal structures through the anal ducts which lead to racemose multiglandular structures located in the perianal tissues, and penetrate the sphincter muscles, especially the internal sphincter. It is known that gonococci may remain alive and virulent for years in the anal structures and that reinfection of the genital tract may occur from the anal focus.

Sulfanilamide, sulfapyridine or sulfathiazole administered orally is effective in the treatment of anal gonorrhea in the absence of localized suppurations or poorly draining sinuses.[138b]

*Chancroid.* This lesion is encountered occasionally in the anorectum and is acquired by the direct inoculation of the streptobacillus of Ducrey through pederasty, or, in the case of women, through contact with the penis during sexual intercourse. The diagnosis can be made fairly readily by smear with the aid of the Unna-Pappenheim stain, and by the vaccine test which is a specific intracutaneous reaction comparable to the Frei test. Sulfanilamide or sulfathiazole are specific for this lesion.[30,84]

*Syphilis.* In the infant, multiple superficial circumanal fissures or shallow ulcers are strongly suspicious of congenital syphilis. Infants may also have condylomata, teeming with spirochetes, on the circumanal area.

In the adult, a chancre may occur anywhere in the circumanal area but it is usually found in the posterior arc of the anal canal. Recently, a chancre occurring in the mucosa of the rectum was reported.[68] The chancre may be acquired through the practice of pederasty, and in the case of women, inoculation may also occur through contact with the penis during sexual intercourse. The diagnosis should be made by dark-field examination. A positive test is conclusive, but a negative one does not exclude syphilis. Secondary syphilitic lesions comparable to the mucous patches in the mouth apparently have not been observed in the rectum. Perianal representation of generalized maculopapular eruptions as well as multiple superficial circumanal fissures comparable to rhagades have been noted. A very characteristic finding is perianal condylomata lata which contain numerous spirochetes.

In late syphilis, gummata, ulcerations and stricture of the rectum have been encountered. The character of these lesions may be altered by secondary infection. Repeated studies and a therapeutic test may be required to establish a definite diagnosis. This especially applies to the diagnosis of syphilitic rectal stricture. The occurrence of tabetic crises of the anorectum is rare. Systemic pathognomonic signs of central nervous system syphilis are usually present in addition to local manifestations, such as relaxation of the anal sphincters, or saddle-shaped perianal anesthesia.

Accepted antisyphilitic treatment should be instituted immediately after the diagnosis is established. In the early cases of anal syphilis the continuous system of therapy is recommended although one may use massive dose arsenotherapy by the intravenous drip method, the so-called 5-day cure.[69] In late syphilis, routine continuous therapy is

preferable. Local treatment is directed to the secondary contamination and infection, if present.

*Vincent's Infection.* This disease is caused by the symbiosis of fusiform bacilli and Vincent's spirillæ. This lesion has been observed on the perineum or in the perianal region. Treatment consists of the topical application of a paste containing of from 5% to 10% of arsphenamine, neoarsphenamine[131a] or mapharsen.

*Granuloma Inguinale.* This lesion is believed to occur in the anal and perianal areas, although recently a rare but apparently proved case of granuloma inguinale of the rectosigmoid with constriction and ulceration has been reported.[29] This is regarded as a disease of the skin and subcutaneous tissues with late or no involvement of lymphatics and lymph glands and is probably caused by the so-called Donovan bodies. These are most frequently found in the tissues (or secretions) with the aid of Dieterle's silver stain. The material from the surfaces of ulcers may also be studied by smear stained by Wright's method.

Tartar emetic administered intravenously or fuadin injected intramuscularly are specific for this lesion.

**Neurologic Investigation of the Colon.** An interesting study of the reactions of the rectal muscle to distention with air was made by Rosenberg and Langworthy.[120] They found contractions of the rectal wall in normal persons in response to sudden stretch; these contractions vary in different patients and may vary in the same patient under different circumstances. In hemiplegia and paraplegia the rectal wall is more resistant to distention. In general, these responses were more pronounced in patients with bilateral injury of the corticospinal fibers. Apparently there occurs a release of tone in the smooth muscle of the rectum from the normal control by the cerebral motor cortex.

Another important study dealing with the neurogenic disturbances of the colon is that of White, Verlot and Ehrentheil.[148] They utilized the colonmetrogram which is the filling curve obtained by slowly distending the colon with warm water; these graphs closely resemble the cystometrograms. The reaction of the colon to filling determines the character of the muscular tone, the alteration in function of the upper or lower motor neuron and whether the effect of a lesion is upon either the sensory or the motor portion of the reflex arc. Colonmetry reflects the motor activity and the sensation of the colon as a whole; it does not indicate circumscribed "disturbances" of the rectum or other portions of the colon.

Lesions of the motor fibers in the brain or in the descending spinal tracts (spastic paralysis) produce a hypertonic response to filling, but lesions in the sacral segments of the cord, cauda equina, or pelvic plexuses (flaccid paralysis) show a hypotonic response (atonic bowel). Colonmetry is also of value in the study of neurologic disturbances of defecation.

**Megacolon.** There is as yet no unanimity of opinion as to the etiology of congenital megacolon.[35] At present, the preponderance of evidence points to an imbalance of stimuli to the colon from the autonomic sympathetic and parasympathetic nervous system[86] as an important cause of this lesion. There may exist either a hyperactivity of the sympathetic or hypoactivity of the parasympathetic nerves or a still undetermined combination of neural influences.

Therapeutic management has made rapid strides in recent years.[81] Daily hot irrigations of normal saline[50] and the employment of parasympathetic drugs are in vogue now. Acetylbetamethylcholine bromide administered orally (in combination with mineral oil) is quite stable in the body and produces prolonged stimulation of the parasympathetic nerves causing increased peristalsis and relaxation of the anal sphincters.[86] The restoration of the normal balance of fluids and electrolytes and the administration of vitamins and of other essential substances of which the body may be deficient or depleted is extremely important.

Surgical treatment is indicated in cases that are not medically tractable as well as for the relief of complications. Sympathectomy or sympathetic ganglionectomy will abolish the inhibitory stimuli of the colon; colonic function will improve and regular evacuations result, but the size of the intestinal lumen does not necessarily decrease as shown by postoperative Roentgen ray studies with the aid of barium sulphate.[13] Spinal anesthesia, by inhibiting the sympathetic stimuli to the colon, may cause evacuations of the colon during the duration of the anesthesia and infrequently for a variable interval of time thereafter.

Children below 3 or 4 years of age constitute poor operative risks and, incidentally, in them the therapeutic benefits are minimal.[35] Patients with thin, weak colons as a rule respond poorly to any type of sympathectomy; in these cases ileoproctostomy followed by graded colectomy is indicated. Segmental colonic resections are useless because progressive dilatation proximal to the point of resection occurs too frequently.

**The Rôle of the Colon in Urogenital Disease.** There exists a close relationship between the intestinal and urinary systems. Pathologic activity of the colon, especially of the anorectum, under certain circumstances may initiate and perpetuate disease in the urogenital tract. The colon in the presence of pathologic activity or deranged function may act as a portal of entry for enteric organisms into the blood and lymph streams; in rare cases a diseased colon may act as a serious focus of infection.[138a]

Apparently the lymphatics constitute an important route for the dissemination of infection from the anorectocolonic foci. There exists a communication between the lymphatics of the anorectum and the urinary bladder[121] as well as between the anorectum and the upper urinary tract.[126] Long ago the existence of a direct lymphatic communication between the right colon and the right kidney was described; it is believed that a similar lymphatic route may exist on the left side.

Uroinfection caused by *B. paradysenteriæ* and allied species have been described. It is believed that uroinfection caused by these enteric organisms may either follow or accompany bacillary dysentery, or occur in patients who present neither a history nor clinical evidence of intestinal bacillary dysentery. Apparently *B. paradysenteriæ* and the allied species causing uroinfection originate in the colon notwithstanding the fact that bacillary dysentery has been regarded as a localized intestinal disease.[38,111a,b]

Uroinfection caused by the organisms of the colon bacillus group occurs frequently in patients who have associated colonic disease or dysfunction. In such patients, Peretz and his associates, by studying

the different antagonistic colon bacillus indexes, found a definite qualitative relationship between the colon bacilli recovered from the urine and the feces. It was concluded that there exists a definite relationship between infection in the urinary tract and the pathologic states in the colon as well as between the types of colon bacillus present in the urinary tract and the colon. Recent studies have shown that in some cases stasis of fecal current and inflammatory and infectious diseases of the anorectocolonic tube are capable of producing and perpetuating moderate and subacute recurrent types of uroinfection which disappeared following the eradication of the intestinal foci.[138a]

The "urologist's ulcer"[65] occurs in men who have received or are receiving massage of the prostate. This ulcer occurs on the mucous membrane of the rectum just above and over the prostate and seminal vesicles; it appears as a raw streaked almost fissured lesion and may undergo malignant degeneration.

*Urogenital Complications of Malignant Disease of the Rectum.* Following resection of the rectum, retention of the urine may occur which eventuates in pyelonephritis in many cases. In men, prostatitis and obstruction at the vesical neck may develop necessitating surgical intervention.[63] In women, contracture of the neck of the bladder is infrequently encountered. Because of lack of normal posterior support, the bladder sags causing an angulation with the urethra that gives a cystoscopic appearance of a moderately advanced cystocele. The bladder distends and becomes trabeculated and cellular; even small diverticula may form. The vesical changes and disturbances are to a large extent also due to direct operative trauma to the bladder and its parasympathetic fibers. The injury may be unilateral, incomplete, transitory, and, occasionally, permanent. The degree of the injury to the nerve supply of the bladder is dependent upon the extent of the malignant involvement and the fixity to adjacent structures.[64,77] The duration of the urinary disturbances depends upon the extent and character of the nerve injury.

**Anesthesia.** The development of several reliable slowly absorbing oil-soluble anesthetic solutions constitutes a significant advance. However, the promiscuous and unintelligent use of these agents constitutes a retreat especially when employed in disregard of the cardinal principles of anorectal surgery.

The long-acting anesthetic solutions have been employed chiefly in the treatment of certain cases of pruritus ani and in selected cases of anal superficial fissures, as well as for the avoidance of postoperative pain and discomfort following hemorrhoidectomy. When used for the avoidance of postoperative pain, the injections must be made under aseptic precautions before the operation is begun. Gorsch advised that the injection of these anesthetic agents be made 24 to 48 hours before operation. There are however numerous competent proctologists who believe that when clean-cut and gentle surgery and meticulous preoperative and postoperative care are employed, there is no need for the long-acting anesthetics (either oily or aqueous solutions); at best these agents are poor substitutes for good surgery.[105]

The slowly absorbing anesthetic solutions are not devoid of hazards and pitfalls. The oil-soluble anesthetic agents may produce an aseptic inflammatory reaction of the tissues into which they are injected eventu-

ating in suppuration and necrosis. The long-acting water-soluble anesthetics, *e. g.*, eucupin-procaine solution, frequently produce edema, hyperemia, and bleeding; "their disadvantages seem to outweigh their advantages."[44] Idiosyncrasy to these drugs is also encountered at times.

The choice of anesthesia for anorectal surgery is of importance. The ideal anesthetic is one that will produce the best relaxation of the muscles of the anal canal and of the perineum. Spinal anesthesia using 5 to 7 mg. of pontocaine in 1 or 2 cc. of spinal fluid or 25 to 50 mg. of procaine hydrochloride crystals dissolved in 1 cc. of spinal fluid which is injected between the third and fourth lumbar vertebræ are the anesthetics of choice, especially when infection in the anorectal tissues is present.[151] The incidence of postspinal headaches has been reduced, if not eliminated, by employing small lumbar puncture needles (22- to 25-gauge) and by keeping the patient in a horizontal position for from 8 to 24 hours after operation. Caudal and paravertebral block is a safe and effective but a difficult and time-consuming procedure even in the hands of the expert anesthetist. The average surgeon prefers low spinal anesthesia to caudal and sacral block because of the simplicity of execution and the promptness of the onset of anesthesia. Infiltration anesthesia using procaine hydrochloride enjoys the widest popularity because it lends itself to office practice. Infiltration anesthesia must never be employed in the presence of infection or in cases of questionable diagnosis. The distortion of the tissues caused by the injection of the anesthetic solution is a distinct disadvantage.[70] Inhalation anesthesia, usually cyclopropane, is employed only when the patient is apprehensive or refuses other types of anesthesia. Deep anesthesia is usually required because the muscles of the anal sphincter are the last to relax.[151] Intravenous anesthesia is infrequently employed for short proctologic procedures, such as incision and drainage of superficial perianal abscesses, the removal of fecal impactions, or gauze packings from deep perineal wounds.[70,151]

**Pruritus.** Intractable pruritus ani remains a problem difficult of solution because of the multiplicity of etiologic factors involved.

*Physiologic Considerations.* The circumanal region in common with the hairy parts of the axilla, labia majora, mons veneris and the areola of the nipple shares a wide distribution of the apocrine sweat glands.[145] These glands develop from the differentiated epithelium and begin to function at puberty. In women the apocrine glands are said to be hyperactive during pregnancy and the premenstrual period, and hypoactive during the intermenstrual phase and after menopause. This obvious relation of physiologic gonadal activity to the function of the apocrine sweat glands suggests that this sweat apparatus is related to, and perhaps is an integral part of the genital tract. The apocrine sweat glands also respond to neural and psychic stimuli.

The secretions of the apocrine glands contain an excess of carbohydrates and proteins and a pH ranging from 6 to 7 in contradistinction to the pH of from 4 to 5.5 of the ordinary sweat secreted by the eccrine sweat glands. The alkaline reaction plus the excess of carbohydrates and proteins of the apocrine secretions are the necessary ingredients for an excellent culture medium for certain bacteria and various fungi.

Other important physiologic considerations concern the disturbances

of fat secretion of the skin,[132] the state of gastric secretion and the pH of the feces.[1]

*General Disease.* The etiologic rôle played by general disease is minimized by some investigators and denied by others. Pruritus ani is occasionally encountered in diabetes mellitus and in pellagra. The rôle of allergy is little understood but frequently incriminated. Although patients with localized pruritus may have an allergic background there is no clear-cut proof that atopy is a necessary prerequisite for its development. However, sensitivity to foods and drugs is important in some cases.

Regional disease in the genital and lower urinary tracts may cause and perpetuate pruritus ani. Disturbances of the intestinal tract resulting in the alteration of the character and pH of the feces, or the presence of intestinal parasites may initiate pruritus ani.

*Psychic Disturbances.* The psychic factors are difficult to evaluate. One of the major problems is to determine what is cause and what is effect. Undoubtedly, localized pruritus can and often does cause nervous symptoms and also may be the last straw in upsetting a delicately adjusted mental equilibrium. From this standpoint localized pruritus is causative. Sulzberger, in agreement with others, asserted that severe pruritus may lead to a "complete disintegration of the morale and occasionally to suicide." On the other hand, pruritus ani undoubtedly can be a local organic manifestation having the same significance as any organ neurosis or hysterical symptom. In this case, the psychogenic factors are primary. In addition to these two thoroughly clear-cut situations we meet with a problem of a pruritus initiated by a local organic factor and the symptoms are utilized in the interest of a psychologic need. The perpetuation of the pruritus then serves as a most important psychodynamic function. This function may represent a substitutive gratification, a displacement to a new erotic zone, or a regression to an archaic erotic zone. Many of the patients in whom one suspects psychic factors fall into the group of obsessional neuroses.[102]

*Anal Lesions.* Accumulating experience shows that the inflammatory and infectious anal lesions as well as pruritus ani in many cases have a common cause in infection of the preformed anal ducts, anal glands and the crypts of Morgagni. A cure cannot be expected unless both the infection of the anal structures and the anal lesions secondary to this infection are removed surgically. In the recurrent cases of pruritus ani following proctologic operation, it is possible that either the local anal lesions or the common underlying cause or both were incompletely eradicated.

*Anal Hygiene.* Poor anal hygiene brought about by fecal staining of the circumanal area is of major importance in the simple cases of anal pruritus; however, anal hygiene *per se* appears to play a minor rôle in the refractory or intractable cases.

*Dermatologic Lesions.* General dermatologic lesions having local anal representation are important causative factors in pruritus ani. Local dermatitis may be produced by the passage of feces containing an excess of skatole or other hydrocarbons[137] or by the therapeutic application of various drugs. The part played by perianal and anal dermatophytid has also received considerations.[12,48]

*Treatment.* The treatment to be successful must be rational and based on sound physiopathologic principles. Because of the multiplicity of factors involved, the intractable or obstinate case presents almost insurmountable difficulties to all forms of therapy.

Rigid cleanliness is very essential. Lilienthal's method of applying bland ointments to the perianal region prior to defecation prevents fecal soiling and is effective in many cases.[87] Soap and other alkali should be interdicted especially in cases where there exists a deficiency of cutaneous fat secretion.[122] Toilet paper containing injurious chemical substances and dyes should be avoided; cotton and olive oil should take the place of toilet paper and soap.

The local application of antiseptic, fungicidal and antipruritic drugs, especially resorcin, cocaine derivatives and mercury, may cause a dermatitis which aggravates the itching.[132] Utmost caution should therefore be exercised when these drugs are employed.

The diet must be bland. If the feces are alkaline in reaction, an acid ash diet should be given, including large quantities of buttermilk[1] or acidophilus milk. In the presence of gastric hypoacidity or anacidity, hydrochloric acid or glutamic acid hydrochloride should be prescribed. The intake of carbohydrates must be reduced to prevent skin hydration which also favors pyogenic and fungous infections.[132] Alcoholic beverages and highly seasoned foods must be absolutely interdicted.

Where food sensitivity is suspected, exclusion diets should be instituted. The intake of drugs, especially phenolphthalein and its derivatives, should be discouraged because of possible sensitivity.

Specific desensitization for perianal moniliasis[49] and dermatophytosis with autogenous or stock vaccine and fungous extract is still in the experimental stage and should be employed with caution because of the occasional alarming reactions.

Radiation therapy may be effective in reducing the hyperactivity of the sweat glands.[122] Perianal hyperhidrosis in certain cases can be controlled by the application of a 4% aqueous solution of formalin.[110]

Of the numerous drugs that have been recommended for the topical application, gentian violet dissolved in water or alcohol, and Castellani's carbolfuchsin solution appear to be the most effective. The injection of oil-soluble long-acting anesthetics into the perianal tissues has afforded a permanent cure in a few and temporary relief in many cases.

Concomitant anorectal lesions, regardless of their etiologic importance in pruritus, should be eliminated in all cases of pruritus ani. When pruritus ani persists despite the foregoing therapeutic measures, radical treatment consisting in the perianal subcutaneous injection of alcohol[16a] or the tattooing of the anal canal and the circumanal area with mercury sulphide[66,138c,140] are required. The injection of alcohol is an established form of therapy and is effective in a large number of obstinate cases. To date, the results from tattooing have been most encouraging except in some cases with dry scaly perianal skin or in patients who had had excessive Roentgen irradiation of the perianal skin. Tattooing with mercury sulphide apparently produces a functional impairment of the cutaneous sensory terminals with a resultant alteration in the capacity of this neural system to respond to adequate stimuli. A change in the cutaneous modalities is produced which,

within limits, is proportional to the amount of intracutaneous deposit of mercury sulphide. This form of therapy is still in the investigative phase.

In the occasional patient with long-standing refractory pruritus ani, after a careful investigation of the psychic factors discussed previously, the guarded use of psychotherapy is of paramount importance. Without entering into the technical details of psychotherapy (which involve considerable difficulties) a warning note should be included: It must never be forgotten that a certain amount of pruritus may be an essential component of the mental equilibrium of the patient considered as a whole. As a corollary of this, a ruthlessly violent removal of so necessary and unconscious gratification can be followed by the most distressing sequelæ, even including self-destroying impulses.

From the foregoing it is apparent that there is no royal road to an easy appraisal and treatment of pruritus ani.

**Hemorrhoids.** The etiology, the comparative value of injectional and surgical therapy and the advisability of immediate or delayed operation for strangulated thrombosed internal hemorrhoids are still matters of controversy.

Infection in the perianal tissues, preceded or accompanied by passive congestion, appears to have gained serious consideration as an important factor in the etiology of piles in many cases. Infection of the crypts of Morgagni, anal ducts and multiglandular structures singly or together may produce perivascular inflammation which is apparently responsible for the formation of hemorrhoids. Campbell's[119] clinical experiment is of interest: he removed the hemorrhoidal varices and purposely left the crypts of Morgagni undisturbed to see if chronic infection which persisted might lead to a recurrence of the piles. In the course of his study he became so convinced of the importance and seriousness of the crypts and the anal ducts that he lost courage to further pursue this study, and began to remove these anal structures routinely during hemorrhoidectomy.

The operation of choice is a non-traumatizing procedure that will eliminate the varices as well as the sources and channels of infection and provide ample drainage through open wounds in order to promote the restitution of the inflamed and infected anal and perianal tissues. The principles of such operation consist of: 1, excision of the crypts of Morgagni and the anal duct-bearing tissues; 2, extension of the wounds originating in the rectum or anal canal into the perianal tissues in order to provide adequate drainage; and 3, keeping the wounds open. The incisions are made in the long axis to the rectum and anal tube and are carried to the perianal skin in a radial manner.

Many surgeons treat irreducible strangulated internal piles (especially when spasm of the anal sphincters is present) by immediate operation;[119b] some surgeons employ palliative measures and defer operation.[51,119a] The Reviewer combines early surgical treatment with the administration of sulfanilamide or sulfathiazole. Chemotherapy is given as an additional safeguard against the remote possibility of occurrence of pylephlebitis or abscess of the liver.

Injectional therapy is the method of choice for moderate sized uncomplicated, soft, bleeding, prolapsing but spontaneously reducible internal piles. Exceptions are made if systemic disease or advanced age pre-

cludes operative interference.[93] Hemorrhoids associated with mild obstructive lesions at the vesical neck may be treated by injection of sclerosing solutions with good chances of success. Good results are also obtained in the treatment of internal hemorrhoids during the early months of pregnancy.

The contraindications to injectional therapy include mixed piles, evidence of recent or old inflammation or infection, neoplastic disease in the anorectocolonic tube or other concomitant local lesions requiring surgical treatment.

The main purpose of injectional therapy is to stop bleeding and to correct the associated prolapse. Following the injection of sclerosing solutions (quinine and urea hydrochloride 5% to 10% solution or 5% solution of phenol in pure almond oil are most popular) submucously or into the hemorrhoidal mass, a sterile inflammatory process is produced within the interstitial tissues of the hemorrhoidal plexus causing a chemical thrombosis of the vessels followed by sclerosis and fibrosis.

The techniques of injection vary with the experience of the operators. The solutions may be injected submucously or into the hemorrhoidal mass. A submucous injection above the anorectal ring about the pedicle of the hemorrhoid will obliterate the superior hemorrhoidal vein and fix the mucous membrane at high level to prevent prolapse.[88] Similar injections of the remaining piles are made usually at weekly intervals until all hemorrhoids have been injected at this high level. Subsequently weekly injections are made into the hemorrhoidal mass at a lower level. Occasionally additional injections have to be made submucously between the treated piles in order to correct mild descensus. Personal experience with this method of injection performed during the past 18 months has been very gratifying.

Properly performed injections should not result in complications. Superficial sloughs are not of serious import, and occur as a result of superficial injection or as a result of the injection of too much solution.[93] Complications such as pain, bleeding, extensive ulcers, irreducible prolapse, strictures, abscess formation with subsequent fistulas, pylephlebitis and septicemia have been reported. It is recognized that this method of treatment is neither simple nor without danger; it has definite limitations which should be understood lest disappointments and complications will result.

Injectional therapy apparently does not produce a permanent cure. Recurrences are dependent on the fate of the fibrosis produced and the elimination of the etiologic factors which had existed prior to the institution of this method of treatment. Since injectional therapy does not remove the original etiologic factors responsible for the development of piles, recurrence can hardly be considered a failure in those instances in which the underlying cause has not been eliminated.

**Anal Fissures (Ulcers).** *Acute Fissure.* Superficial, single or multiple fissures in the anal canal or circumanal area are usually produced either by trauma or irritation. These fissures show no adjacent inflammation or induration. They either heal spontaneously or with the aid of the topical application of bland ointments. Occasionally the long-acting oil-soluble anesthetic solutions are used to allay pain.

*Chronic Fissure.* This lesion consists of an ulcer with adjacent induration and inflammation[144] and dysfunction with fibrosis of the subcu-

taneous portion of the external anal sphincter muscle. The underlying cause of the chronic fissure (ulcer) resides in infection of the preformed anal ducts and crypts of Morgagni.[16a] The frequent occurrence of this lesion in the posterior arc of the anal canal is due to the preponderance of crypts of Morgagni in the posterior portion of the anal canal.[108]

An attempt has also been made to explain the pathogenesis of the anal ulcers on the basis of the anatomic arrangement of the various components of the external sphincter muscle. The superficial portion of the external anal sphincter muscle has a Y-shaped origin and insertion and lies above and external to the subcutaneous component of the external anal sphincter which is an unsupported circular muscle surrounding the anal orifice. Thus the subcutaneous portion of the external anal sphincter lies like a "bar across the crook of the Y" and is therefore subject to frequent trauma.[10a]

Chronic anal fissures (ulcers) are best treated by wide excision of the ulcer-bearing area, including the involved crypt or crypts (and the sentinel pile, if present) followed by the division of the subcutaneous portion of the external anal sphincter muscle. The long-acting water- or oil-soluble anesthetics have no place in the therapy of this lesion because they are ineffective and dangerous. The operative treatment, because of the smooth convalescence and the inevitable successful issue is definitely preferable to taking even the slightest risk with the slow absorbing anesthetic agents.[144]

**The Pecten Band.** Pectenosis has been regarded as a pathologic entity which is characterized by a circular constriction caused by a deposit of fibrous tissue in the submucosa at the pectinate line, and is said to be produced by chronic passive congestion. Its counterpart is sometimes found in globus hystericus when fibrous tissue in the submucosa forms opposite the cricopharyngeus muscle. A recent important study[45] showed that the submucosa in the region of the pectinate line contains involuntary muscle fibers continuous with the muscularis mucosæ of the rectum, which, in some cases, form a well-developed submucosal muscle close to but always distinct from the internal anal sphincter muscle. The term "muscularis submucosæ ani" was proposed for this submucosal layer of muscles. The rôle played by this muscle is not that of a fibrous band, as hitherto believed, but that of a muscle band exerting its effect through either spasmodic contraction produced by local irritation or hypertrophy resulting from chronic spasm and leading to stenosis.

Apparently this submucosal muscle had hitherto been overlooked by histologists. This is the explanation given by C. N. Morgan for the absence of reference to this muscle in his otherwise authoritative description of the anatomy of the anal canal.[108]

**Anal Abscess and Anal Fistula.** The now well-recognized concept that these lesions originate from an infection in the preformed anal ducts[16a] is worthy of reëmphasis. The anal ducts empty in the crypts of Morgagni but may lead to racemose multiglandular structures situated in the perianal tissues and may pierce the anal sphincter muscles, especially the internal sphincter. The anal ducts are lined with a secreting columnar epithelium which in branches is cuboidal, and may become natural incubators for bacteria under suitable conditions. Infection of these anal structures may lead to the development of peri-

anal and perirectal suppurations eventuating in anal fistulas. The primary openings of true anal fistulas are always found within a crypt of Morgagni.

Perianal fistulas occurring as a complication of regional ileitis have been reported.[118] The accompanying infectious diarrhea is believed to produce infection in the crypts of Morgagni which in turn results in anal fistulas in most of these cases; in some instances, however, there occurs direct fistulization from the ileum to the rectum or perirectal tissues, which may become infected anywhere along its tortuous course.

Anal and perianal abscesses should be incised widely and drained adequately as early as possible. The T-shaped or crucial incisions with the removal of the skin and the infected deeper tissues between the crossed incisions (thus unroofing the abscess cavity) are most often employed. The abscess cavity is explored digitally and multilocular cavities, if present, are broken up and packed lightly with either iodoform or plain gauze. Fistulectomy combined with incision and drainage of the abscess may be performed in selected cases.

The fundamental principles of fistulectomy consist of the clean-cut excision of the fistulous channel with the adjacent infected tissues; the elimination of overhanging skin edges to promote adequate drainage, and the employment of light gauze packing for about 48 hours. Of equal importance is the correct and meticulous postoperative care.[10b,16a,c]

Extensive fistulas may require two-stage operations. At the first procedure, the fistulous tract or tracts are excised down to the sphincter muscles. The remaining portion of the channel is threaded with a seton and tied loosely. At the second operation, which is performed after a firm scar had formed in the lateral wound, the sphincter muscle is divided and the remaining portion of the fistulous tract is laid open.[10b] This procedure prevents the wide retraction of the cut sphincter muscle with resultant anal incontinence.

**Anal Incontinence.** In general, this complication follows either obstetric procedures or operations upon the anal canal; it occurs most often following fistulectomy. In most cases, if not in all, anal incontinence is a product of unforgivable incompetence.[10b] Numerous plastic procedures have been devised. The Wreden-Stone operation utilizes two fascial slings to encircle the anal canal which are anchored to the glutei maximi. Buie advocates a simple plastic procedure which consists of the excision of the scar tissue and the recreation of the original wound which was present immediately after fistulectomy.[16a] Meticulous postoperative care results in a competent healthy scar. Blaisdell developed an ingenious and simple procedure which consists in isolating and reefing the external anal sphincter muscle thus decreasing the circumference of the whole muscle and the anal outlet.[10c] Excellent results have followed the performance of this procedure. Knapp, in a selected case of incontinence, successfully utilized the superficial transverse perineal muscle for the repair.[82]

**Injuries of the Anus, Rectum and Sigmoid.** Small particles of food and foreign bodies, such as fish bones, seeds, and so forth, may lodge in a crypt of Morgagni and result in infection of the crypt requiring surgical intervention. Foreign bodies lying free in the lumen of the rectum, such as enema tips, usually present no difficulties in their removal.

Impalement of the rectum is a serious condition. The prognosis

depends on the path of injury and the extent of visceral involvement. Immediate exploratory laporotomy is usually performed when perforation of a viscus has occurred. Expectant treatment and the performance of an occasional colostomy is indicated in extrarectal impalements with or without extensive perineal laceration.[28]

Contrary to the general consensus, perforations of the rectum or sigmoid occurring during sigmoidoscopic examination may be treated conservatively, especially when the patient is a poor risk because of advanced age or concomitant disease, or in those instances where a delay in establishing a diagnosis has occurred.[122]

**Pediatric Proctology.** As in the adult, proctosigmoidoscopic examination of infants and children is indicated in the presence of symptoms, such as bleeding, diarrhea, constipation, protrusion, tenesmus, or pruritus.[33a,115a] The presence of an obstructive lesion that prevents the insertion of the examining finger or the instrument into the anorectal outlet constitutes the only contraindication to sigmoidoscopy.

In infants and young children, the rectum is in a vertical position and the sigmoid may be long and tortuous with a sharp angulation either to the right or to the left of the pelvis; the bowel is very fragile and may be easily traumatized. Either morphine[115a] or general anesthesia[33a] is employed in most cases of infants or young children. However, in many children over 5 years of age, the examination may be carried out easily without the aid of either morphine or anesthesia. The employment of inflation of the bowel as an aid to sigmoidoscopy is a matter of personal preference and experience; it is considered safer to visualize the lumen of the colon before advancing the sigmoidoscope, which is best accomplished by gentle inflation. The original or a modified inverted position is considered the most suitable for sigmoidoscopy in infants and children.

Juveniles, like adults, are subject to inflammatory bacterial or parasitic disease, suppurations, fistulas and fissures *in ano*, prolapse of the rectum, benign and malignant polyps and other tumors. Unlike adults, infants and young children seldom have internal piles but more often present congenital malformations of the anus and rectum.

**Miscellaneous Considerations.** *Clinical Pathology.* The microscopic study of the bowel discharges at the time of proctosigmoidoscopy has become a routine procedure in many offices and clinics. The presence of cellular exudates in the bowel discharges is indicative of lesions associated with anatomic changes in the wall of the colon.[8] The determination of the reaction of the feces is of importance.[1] The approximate pH of the feces can be established with the aid of nitrazene paper. Normal stool is acid in reaction.[143] The sedimentation time of erythrocytes is another simple office procedure.[139] The fact that the sinking of the red blood cells is accelerated in the presence of hidden suppurations in the anorectal tissues makes this test valuable in the differential diagnosis of acute anal pain and in the differentiation of an inflammatory reaction from a suppurative process following the injection of the long-acting anesthetics. The Frei test is at present performed routinely in all cases of diarrhea, rectal strictures and whenever the diagnosis is obscure.

*Ambulatory Operative Treatment.* Perianal hematoma (external thrombosed pile), subacute fissures and short subcutaneous sinuses or fistulas are suitable for ambulatory operative treatment.[2,18] The surgeon performing ambulatory operations for anorectal lesions should

provide adequate office facilities for immediate postoperative rest and care, and proper supervision at the patient's home.

It is generally conceded that the published good results of ambulatory operative treatment of proctologic lesions do not represent a fair cross-section of the work done throughout the country. That better results follow operations performed in a hospital can hardly be gainsaid;[72] ambulatory surgical treatment is usually incomplete in scope and hence only palliative in character.

*Sacrococcygeal (Pilonidal) Cysts and Sinuses.* In spite of numerous studies there is still no unanimity of opinion as to the essential aspects of this lesion. Most investigators agree that the sacrococcygeal lesion is congenital in origin and that it arises from the ectoderm. They disagree as to whether nerve tissue or integument is the source of origin. The tendency to recurrence characterizes this lesion regardless of the form of surgical procedure utilized. Non-surgical procedures (injectional sclerosing therapy) are still on trial. The occasional concomitant occurrence of a malignant lesion[57] and postinjection sloughs favor clean-cut surgery.

Radiation therapy is advocated as a substitute for operation for the recurrence of infected sacrococcygeal sinuses.[138] It is conceivable that when all branches of the sinus and the ectopic epithelium are incompletely removed during the original operation, radiation therapy may fail, and reoperation may become necessary.

*Rectal Bleeding.* Bleeding from the rectum usually demands a complete survey to establish its source. Internal hemorrhoids are the most frequent cause while neoplasm is the most important. Profuse bleeding following the inexpert injection of sclerosing solutions for the treatment of internal piles and prolapse occurs infrequently;[17] the incidence of this complication cannot be surmised from the perusal of published reports. Blood originating from a lesion in the descending or sigmoid colon if retained in the rectum long enough may appear dark, resembling blood coming from a lesion in the upper intestinal tract or stomach, while, in the case of hypermotility of the intestines, blood coming from a gastric or duodenal lesion may occasionally be bright red. Rarely, bleeding in children may originate from an ulceration in a Meckel's diverticulum with or without aberrant gastric mucosa, or from an ulceration of misplaced gastric mucosa in the rectum.[43,46]

Blood dyscrasias, such as thrombocytopenic purpura and vitamin C and K deficiencies may be the underlying cause in many cases of occult or gross bleeding from the colon and rectum. Bleeding noted in diarrheas is frequently an expression of subclinical hypovitaminosis and not necessarily caused by the inflammatory or infectious process of the bowel.[92] Colonic bleeding noted in advanced Bright's disease and uremia may be due to vitamin K deficiency.[23]

*Effects of Irradiation on Rectum.* Following radiation therapy (radium, Roentgen ray, or both) for malignant lesions of the urogenital tract there may develop changes in the rectum (as well as in other segments of the colon and small intestine) ranging from mild mucosal injury to ulcerations.[136,149] The ulcerations may either erode the bowel wall and eventuate in perirectal suppuration or rectovaginal fistulas or terminate in healing with intense fibrosis leading to partial or complete stenosis. On the other hand, the perirectal structures may be primarily affected causing secondary involvement of the rectum. The

simple lesions may either be self-limited or may respond to conservative measures. The advanced lesions, *e. g.*, ulcerations or stenosis, may require temporary or permanent colostomy. The present consensus is against dilatation of the strictures because perforations are apt to follow this maneuver. Severe pain may be controlled by the resection of the presacral nerves.[136]

*Colonic Allergy.* The reactions produced in the colon by allergy to foods have been experimentally demonstrated in humans to consist of edema, hyperemia and increased secretion.[3,59,60] Histologically this reaction is represented by marked edema of the submucosa and cellular infiltration. These phenomena are produced partly by the direct contact of the offending food with the mucosa and, more importantly, by the allergen reaching the mucosa *via* the blood stream after absorption. Observations similar to the foregoing as well as spasm frequently encountered during proctosigmoidoscopy should suggest a possible allergic etiology and lead to further investigations.

*Enterobiasis.* The introduction of cellophane-tipped swabs constitutes a distinct advance in the study of pinworm infestations. Of equal importance is the therapeutic employment of the recently proposed enteric coated gentian violet.[154] This therapeutic agent is believed to be the most efficacious drug now available for the treatment of enterobiasis. While the treatment of individual patients has become relatively simple, the eradication of the pinworms occurring in several members of a family or in inmates of an institution is still a difficult problem.[34] This difficulty is caused by the high incidence of reinfection.

Acute appendicitis caused by *Enterobius vermicularis* is infrequently encountered. Occasionally several members of the same family may have pinworm infestation and acute appendicitis concomittantly.[103]

*Intestinal and Vaginal Trichomonas.* Recent studies fail to support the common belief that trichomonads infecting the vagina are of intestinal origin. Experimentally, human and monkey vaginas cannot be infected with intestinal trichomonads.[76]

*Fecal Impaction.* Fecal incontinence from accumulation of feces in the rectum occurs infrequently after operations; in the debilitated bedridden individual; following the use of barium sulphate for diagnostic purposes, or after the eating of roughage.[7,106] The incontinence manifests itself as a continued discharge or diarrhea. The treatment consists of the administration of warm oil as retention enemata and the gentle digital removal of the impacted feces. Occasionally hydrogen peroxide enemata and the instrumental removal of the feces must be resorted to.

*Mineral Oil.* A recent provocative paper by Morgan deals with the misgivings on mineral oil.[109] Mineral oil is believed to interfere seriously with the physiology of defecation; it apparently causes the premature passage of feces from the transverse, descending and sigmoid colon, the true fecal reservoir, into the rectum. There the stool may be abnormally retained as the admixture of the oil with the feces prevents their complete evacuation. Mineral oil interferes with the healing of wounds following anorectal operations and may induce bleeding. Liquid petrolatum, by causing increased motility of the intestine and rapid transportation of food prevents its proper digestion and absorption and has a deleterious effect on the fat-soluble vitamins A, D and K.

Curtis and Kline[32] found that the feeding of crystalline carotene in

vegetable oil to normal persons produces a rise of the concentration of carotene of the blood, and that a reversal of this effect occurs when mineral oil is fed with the carotene. They also demonstrated that the feeding of mineral oil 2 or 3 times daily before meals prevents the rise of the blood carotene following the partaking of a high carotene diet. However, no effect on the blood carotene occurs if the mineral oil is administered only before retiring when no food is ordinarily taken. This study shows that mineral oil mixed with food in the gastro-intestinal tract inhibits or prevents the absorption of carotene.

*Gastro-intestinal Manifestations of Anorectal Lesions.* As a rule, lesions of the anorectum produce a characteristic local symptom complex which is easily differentiated from that produced by disease in the upper digestive tract. However, in certain instances anorectal disease may cause referred abdominal symptoms suggesting disease of the stomach, appendix or the biliary tract. Recently, Gauss[54] called attention to the irritable colon and gastric irritation syndromes produced by disease in the anorectum (13 of his 15 patients responded promptly to proper proctologic therapy). The symptomatology of some of his patients included heartburn which occurred several hours after meals and was relieved by food or alkalies. Apparently the anorectal lesion produces irritation of the colon which in turn may produce the gastric irritation syndrome. This effect is mediated through the sympathetic and parasympathetic nerves of the autonomic nervous system.

*Rectal Absorption of Sulfanilamide and Its Derivatives.* Recent experimental studies proved that sulfanilamide is absorbed from the rectum and colon in man when administered either in solution[141a] or in suppository.[141b] The concentration of sulfanilamide in the blood after the suppositories was inadequate, but the solution gave a concentration comparable with that resulting from the oral administration. The rectal route of administration of sulfanilamide is recommended whenever the oral route cannot be utilized. The same total dosage may be employed for the rectal as for the oral administration. The rectal route has been employed successfully in the treatment of anorectal manifestations of venereal lymphogranuloma[95] and in chronic ulcerative colitis[27,141b] (Protocol 4).

The rectal administration of sulfapyridine in suspension has been employed successfully in the treatment of pneumococcic pneumonias.[150] The dosage required to produce an adequate concentration of sulfapyridine in the blood was 3 times larger than the oral dose. Nausea was almost eliminated.

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# OPHTHALMOLOGY.

UNDER THE CHARGE OF
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## TREATMENT OF THROMBOSIS OF THE RETINAL VEINS.

Thrombosis of the central vein of the retina or one of its branches or tributaries is a rather frequent cause of loss of vision in middle aged or elderly individuals. Its frequency is considerably greater among patients with relatively benign hypertensive disease than it is in the general population or in patients with severer forms of hypertensive disease. The majority of patients who present themselves with loss of vision due to thrombosis of a retinal vein are in other respects in relatively good physical condition; so that the loss of vision is their primary concern. The average age of occurrence of this type of vascular accident is 57 years, so that many of these patients have the expectancy of a number of years of active life. It would seem, therefore, that any form of treatment would be worth while which would offer a chance of restoring useful vision to the affected eye. In the past, little has been offered to these patients in the way of treatment other than general measures for the control of the hypertensive disease, if present, and potassium iodide. However, in 1930, Löwenstein and Reiser[8] suggested Roentgen ray therapy to the affected eye, and, in 1938, Holmin and Ploman[6] reported the use of heparin in the treatment of a case of thrombosis of the central vein of the retina. Though reports of the results of these two types of therapy have been rather few to date, it was thought that it might be of interest to compare the visual results obtained with those in essentially untreated cases.

In a series of 26 cases of thrombosis of a tributary retinal vein reported by Moore in 1924, the last recorded vision was 6/60 or less in 14 (54%), between 6/36 and 6/12 in 10 (38%), 6/6 in 1 (4%) and unrecorded in 1. Considering only the 12 cases in which vision was recorded at least 1 year after the occurrence of the thrombosis, the final visual acuity was 6/36 or less in 8 cases (67%), between 6/24 and 6/12 in 3 (25%), and 6/6 in 1 (8%). In a similar series of 29 cases reported by Jensen[7] in 1936, visual acuity at the end of a year or longer was 6/36 or less in 14 (49%), between 6/24 and 6/12 in 9 cases (31%), 6/9 in 3 (10%), and 6/6 in 3 (10%). Combining these two series, it is apparent that useful vision was obtained or retained in 19 of 41 cases (46%) and normal vision in 4 (10%). Secondary glaucoma did not develop in any of the 31 cases of thrombosis of a tributary retinal vein reported on by Moore.[11] It developed in only 1 of a series of approximately 50 cases reported on by Uhthoff, and in only 1 of Jensen's 54 cases.

The final acuity of vision obtained in untreated cases of thrombosis of the central vein is usually considerably poorer than it is in cases of thrombosis of tributary veins. Thus, among the 19 cases with records of vision in Moore's series, the last recorded vision was 6/60 or less in

17 (90%), 6/36 in 1 (5%) and 6/24 in 1 (5%). Among the group of 10 cases which were observed for more than a year, the last recorded vision was less than 6/60 in all. So that useful vision was not obtained or retained by any patient in this group. Secondary glaucoma developed in 10 of Moore's 31 cases of thrombosis of the central vein (32%), and in 12 of Uhthoff's 50 cases (24%).

Stimulated by a report of Hessberg's on rapid and complete absorption of hemorrhages in the retina following irradiation of the eye, Löwenstein and Reiser[8] decided to try the effect of medium and small doses of Roentgen ray on thrombosis of the retinal veins. They thought originally that the rays might have a direct thrombolytic action and that they might stimulate the formation of collateral circulation. Later, however, they decided that these two effects could not be demonstrated. They concluded that the essential effect of the Roentgen rays was that of vasodilatation by which an active hyperemia was produced which increased the rate of absorption of the hemorrhagic extravasations. They thought also that the increased vis a tergo resulting from the vasodilatation would prevent the thrombus from becoming completely occlusive if it were not so originally. They suggested also that Roentgen ray therapy might prevent the development of secondary glaucoma by decreasing the secretion from the ciliary body. They reported 1 case of thrombosis of the central vein in which the vision was 6/20 at the time treatment was started. One year later the vision was 6/5. Also, in a case of thrombosis of a tributary vein the vision, which had been 6/20 at the onset, was 6/4 at the end of $4\frac{1}{2}$ months.

Löwenstein and Reiser thought that irradiation of the eye was indicated especially in cases in which a specific tuberculous or syphilitic affection of the intima of the vein was the basic cause of the thrombosis. They expressed doubts that this method of treatment would be of any value in cases of thrombosis of the central vein in which the obstruction was caused primarily by thickening of the connective tissue in the lamina cribrosa or in cases of tributary vein thrombosis in which the obstruction resulted from compression of the vein by a sclerosed arteriole.

In 1932, Schnyder and Forster[16] reported on the treatment of 7 cases of thrombosis of retinal veins by irradiation according to the method of Löwenstein and Reiser but using somewhat smaller doses. Two of the cases showed complete thrombosis of the central vein. In 1 of these, only slight residuals were visible ophthalmoscopically after 6 months and the vision was 6/10. In the other, the hemorrhages were completely resorbed after 8 months and the vision was between 6/10 and 6/12. There were 3 cases of thrombosis of a tributary of 1 of the main temporal veins without much disturbance of vision. At the end of 3 months all the hemorrhages had been resorbed in 2 of these cases and most of the hemorrhages in the other. In 1 case the main superior temporal vein was thrombosed and there were extensive hemorrhagic extravasations involving the macula. At the end of 5 months, only a few residual hemorrhages were present and the vision was between 6/12 and 6/10. The seventh patient had had a thrombosis of the superior temporal vein of the right retina 3 years previously. The hemorrhages had been completely resorbed after 27 months, but as a result of consecutive retinal and optic nerve atrophy the vision remained

reduced to ability to count fingers at 2 meters. When thrombosis occurred in the superior temporal vein of the left retina, the eye was irradiated. The hemorrhages were almost completely resorbed at the end of $5\frac{1}{2}$ months and the vision was between 6/12 and 6/10. The results in this series would seem to be considerably better than the average obtained in the untreated cases.

Schnyder and Forster stated that, in all 7 cases, they had the impression that as a result of the Roentgen ray therapy the hemorrhages absorbed considerably more rapidly and completely than was usual in cases of thrombosis of the retinal veins. They noted that in 2 cases, 1 of central vein and the other of tributary vein thrombosis, venous thrombosis with hemorrhages and detachment of the retina developed in the periphery of the retina some time after the irradiation therapy had been concluded. In both of these cases spontaneous healing took place, but Schnyder and Forster thought that the lesion was caused probably by a tear of the retina resulting from the hyperemia and consecutive edema produced by the irradiation. Therefore, they were inclined to think that the treatment was not entirely harmless and that it should be reserved for those cases in which the completeness of the thrombosis and the extent of the hemorrhages make the prognosis for recovery of vision doubtful if the condition is untreated.

Later reports on the results of irradiation treatment have not been so encouraging. In a discussion at the 1936 meeting of the German Ophthalmological Society of Czechoslovakia, Braun[3] and Ascher[1] stated that Roentgen therapy did not seem to influence the course of cases of complete thrombosis of the retinal veins though it might have a favorable effect on cases of partial or incomplete thrombosis. In 1937, Gradle[5] published the results obtained by irradiation in a series of 16 cases. He was particularly interested to see if this type of treatment was of any value in preventing the development of secondary glaucoma, a point which had not been considered by the other authors. He used 3 to 6 exposures of filtered rays up to the extent of one-fourth to one-third of a skin erythema dose. He did not use pilocarpine as a prophylactic in this series. The results obtained were compared with those in a series of 21 untreated cases which had been observed over a similar period of time. Pilocarpine was used as a prophylactic against the development of secondary glaucoma in the cases of thrombosis of the central vein in this second group. The cases in each group were observed over periods ranging from several weeks to 10 years.

Among a group of 14 cases of thrombosis of a tributary vein in which irradiation was not used, the vision at the time of the last examination was 6/30 or less in 7 (50%), 6/12 to 6/10 in 6 (43%), and 6/5 in 1 (7%). Among a group of 7 cases of thrombosis of a tributary vein in which irradiation was used, the vision at the last examination was 6/30 or less in 5 (72%), 6/20 in 1 (14%) and 6/5 in 1 (14%). Among a group of 7 cases of thrombosis of the central vein in which irradiation was not used, the vision at the last examination was 6/30 or less in 6 (86%) and 6/6 in 1 (14%). Among a group of 9 cases of thrombosis of the central vein in which irradiation was used, the vision at the last examination was 6/30 or less in 7 (78%) and 6/15 in 2 (22%). Essentially, then, the final vision obtained differed very little in the two groups of cases. Irradiation was not entirely successful either in the prevention or the development of secondary glaucoma. Glaucoma developed in

1 (7%) of the untreated cases of tributary vein thrombosis and in 1 (14%) of the untreated cases of central vein thrombosis. In both of these cases, the glaucoma was bilateral and was of the chronic simple or compensated type and may have developed independent of the thrombosis. Glaucoma did not occur in any of the 7 cases of tributary vein thrombosis which were irradiated, but typical acute incompensated glaucoma developed in 1 (11%) of the 9 irradiated cases of central vein thrombosis.

In summary, Gradle stated that he did not think that irradiation accelerated the absorption of the hemorrhages or that it improved the end result so far as vision was concerned. He expressed the opinion that irradiation might be of some value in the prevention of secondary glaucoma.

In view of the rather conflicting reports on its efficacy, Roentgen ray treatment may be worthy of further trial in the treatment of retinal venous thrombosis. I regret that a rather extensive report on this method of treatment which was published in *Ophthalmologica* for June-July, 1940, is not available to me for review at the present time.

In March, 1938, Holmin and Ploman reported the results obtained in a case of thrombosis of the central vein of the retina which they treated with heparin. The vision shortly after the onset of the thrombosis was 6/30. Heparin therapy was started 41 hours after the onset. Three to four daily doses of 1.66 mg. per kilo of body weight were given during a period of about 10 days. The ophthalmoscopic picture did not change materially during the time of administration of the heparin but the vision improved to 6/7. During the following weeks the hemorrhages absorbed gradually. At the end of 3 months the vision was 6/6.

Ploman[13] had studied previously 13 cases of thrombosis of the central vein. Nine of these had become blind, 8 from secondary glaucoma, 1 from proliferating retinitis and detachment of the retina. Final vision in 1 was hand movements, in 2, 6/60, and in 1, 6/20.

In Ploman's opinion, the obstruction to the bloodflow in the case treated with heparin was not complete at the time he saw the patient. In most cases, he thinks, clots accumulate on the thrombus and finally produce complete obstruction. Heparin prevents this further growth of the thrombus and permits retraction of the fibrin already present in the clot so that the obstruction to the circulation is reduced. Ploman thinks also that the heparin may diffuse through the capillary walls and into the tissues so that they become heparinized. As a result, the blood in the hemorrhagic extravasations in the retina remains more liquid and can be resorbed more rapidly.

In July, 1938, Boström and William-Olsson[2] reported a second case of thrombosis of the central vein of the retina treated with heparin. The heparin was not started in this case until about a month after the occurrence of the thrombosis. Vision at the time of first examination was 6/60. Heparin was given intermittently for 20 days. At the end of 1 month the retinal lesions had improved considerably and vision was 6/10. In discussing the rationality of the treatment, the authors stated that in intravascular thrombosis the thrombus acts as a foreign body, producing kinase and a tendency to coagulation in its neighborhood. Heparin lessens the tendency to coagulation. This prevents growth of the thrombus and allows the coagulum to retract so that

parietal canalization may occur. Later the thrombus itself may be dissolved by proteolytic enzymes.

In June, 1938, Ploman reported his further experiences with heparin treatment of thrombosis of retinal veins. He used, in hospital cases, a daily dose of 250 mg. divided into 4 doses and, in out-patients, 200 to 300 mg. daily in 2 doses. Treatment was continued for from 5 to 10 days. Two additional cases of central vein thrombosis were treated. In 1 of these at the end of 3 weeks the ophthalmoscopic appearance was considerably improved and vision had increased from hand movements to finger counting at 4 meters. In the other, after 6 weeks' treatment with potassium iodide, vision had decreased from 6/8 to 6/9. One month after 3 days of heparin treatment the vision was 6/6. He treated also 6 cases of tributary vein thrombosis. In 1 of these there was no improvement, and the vision was still 6/60 at the end of 6 weeks. In another, vision improved from 6/20 to 6/9 in 2 weeks, but 1 week later a second thrombosis occurred which reduced the vision again to 6/20. Heparin did not help this second thrombosis. In the other 4 cases, improvement was noted. The final recorded vision was 6/20 in 2 cases, 6/10 in 1, and 6/9 in 1. The period of observation in these cases was rather short, 6 weeks or less in all but 1 case. For comparison, Ploman gave the results at the end of 3 months in 26 cases of tributary vein thrombosis treated with potassium iodide. Among these 26 cases, 4 were worse, 12 were unchanged and 10 were improved. The mean improvement in vision was 0.2. The mean improvement in vision in heparin treated cases was 0.3. Ploman admitted that the period of observation in these cases was too short to permit any conclusions as to final results.

Ploman used heparin in the treatment also of 1 case of hemorrhage in the retina (type not stated) in which the vision improved in 2 weeks from 6/15 to 6/6, and in 1 case of hemorrhage into the vitreous in which the vision improved from counting fingers at 2 meters to 6/7 in 1 month.

In April, 1941, Rea[14] reported the heparin treatment of 3 cases of complete thrombosis of the central vein and of 2 cases of tributary vein thrombosis. He stated that one of the eyes with central vein thrombosis became glaucomatous and completely blind. Some improvement was noted in the 2 other cases. In 1 case, vision improved from 2/60 to 6/24. The 2 cases of tributary vein thrombosis were completely cured with vision of 6/6. Rea thought that the treatment produced good results if it was started the same day as the occurrence of the thrombosis or "immediately afterward;" but that, when there was a delay of several days in starting the heparin, the results were not good.

At the 1940 meeting of the American Ophthalmological Society, MacDonald[9] reported the results obtained by the use of heparin in 1 case of thrombosis of the central vein of the retina and in 1 case of thrombosis of the macular branch of the superior temporal vein. In the case of central vein thrombosis, treatment was started 2 weeks after onset when vision was ability to count fingers at 2 meters. Heparin was given by the continuous drip method and the clotting time was kept at or above 30 minutes for 5 days. At the end of 6 months, vision was 4/36. Numerous punctate hemorrhages were present in the retina. In the case of tributary vein thrombosis treatment was started 3 months after the onset of the thrombosis when vision had decreased from 6/36

to 6/60 and the hemorrhages had increased in number. Heparin was given by the continuous drip method and the clotting time was kept at or above 20 minutes for 5 days. At the end of 6 weeks vision was 6/18 and no new hemorrhages had occurred.

In the discussion of MacDonald's paper Gifford[4] stated that he had treated 2 cases of thrombosis with heparin without improvement in vision. Treatment was started 1 month and 2 weeks after the occurrence of the thrombosis, respectively. Rychener[15] reported on 5 cases of thrombosis of the central vein; heparin was given intermittently (without laboratory control of the clotting time) in 1, and by the continuous drip method in the other 4, the clotting time being kept at approximately 15 minutes. The final vision obtained was less than 6/60 in 4 cases, and 6/20 in 1 case. He treated also 2 cases of tributary vein thrombosis. Final vision was 6/10 in 1 case and 6/6 in the other.

In his paper, MacDonald called attention to the apparently spontaneous cure of an occasional case of thrombosis of the central vein in a young individual. He mentioned cases reported by Mathewson[10] and by Parker[12] in which 6/6 vision was regained in 1 year and 16 months respectively. In the discussion Verhoeff[17] stated that, in his opinion, most cases of so-called "thrombosis of the central vein" in elderly individuals are really obstructions of the vein caused by obliterating endophlebitis and that actual thrombosis occurred only rarely and then in young individuals. I am inclined to think that either of these types of occlusion of the vein may occur without any definite age limitations and that the prognosis is relatively good in the cases of true thrombosis and essentially hopeless in the cases of obliterating endophlebitis or phlebosclerosis. If a differential diagnosis between these two types of lesion could be established clinically, the indications for the use of heparin would be more clearly defined and, perhaps, the results of treatment in selected cases would be more uniform.

TABLE 1.—VISUAL RESULTS IN THROMBOSIS OF THE CENTRAL VEIN OF THE RETINA.

| | No. of cases. | Vision. | | |
|---|---|---|---|---|
| | | 6/30 or less. | 6/20 to 6/10. | 6/7 to 6/6. |
| Untreated | 42 | 36 (86%) | 2 (5%) | 4 (9%) |
| Irradiation | 12 | 7 (58%) | 4 (33%) | 1 (9%) |
| Heparin | 14 | 8 (58%) | 3 (21%) | 3 (21%) |

Reference to Tables 1 and 2 will show that, though the number of treated cases is rather small, there does seem to be a definite improvement in the visual end results with either irradiation or heparin therapy with the results a little in favor of the heparin. Thus, in cases of central vein thrombosis, vision of 6/20 or better was obtained in only 14% of the untreated cases, in 42% of the irradiated cases, and in 42% of the heparin treated cases. In the cases of tributary vein thrombosis, vision of 6/20 or better was obtained in 49% of the untreated cases, in 62% of the irradiated cases, and in 91% of the heparin treated cases.

TABLE 2.—VISUAL RESULTS IN THROMBOSIS OF TRIBUTARY RETINAL VEINS.

| | No. of cases. | Vision. | | |
|---|---|---|---|---|
| | | 6/30 or less. | 6/20 to 6/10. | 6/7 to 6/6. |
| Untreated | 68 | 35 (51%) | 28 (41%) | 5 (8%) |
| Irradiation | 13 | 5 (38%) | 3 (24%) | 5 (38%) |
| Heparin | 11 | 1 (9%) | 7 (64%) | 3 (27%) |

McCullough, of Toronto, has told me personally of favorable results in cases of retinal vein thrombosis treated with heparin. Personally, I have observed recently a case of thrombosis of the central vein treated with heparin in which the hemorrhages had been completely absorbed from the retina within 6 months after the onset, and vision had returned to 6/6. In fairness, however, I should state that during essentially the same period, another case of thrombosis of the central vein cleared up completely under treatment only with potassium iodide and vision of 6/6 was regained in this case also. On the basis of the results reported so far, it would seem well worth while to try these methods of treatment in cases of thrombosis of either the central or a tributary retinal vein if the case is seen reasonably soon after the occurrence of the thrombosis.

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